Riluzole-triazole hybrids as novel chemical probes for neuroprotection in Amyotrophic Lateral Sclerosis.

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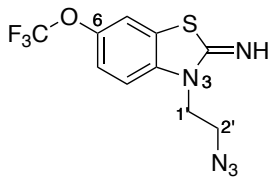
Supporting Information

General methods

Unless otherwise stated, all reactions were carried out under an inert atmosphere of dried nitrogen, in glassware which had been oven-dried. Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fisher Scientific, TCI UK or Lancaster Research Chemicals and were not purified except where stated. Solvents were purchased anhydrous and stored over molecular sieves. Thin layer chromatography was performed on aluminium sheets coated with Merck silica gel 60 F254 with visualisation using potassium permanganate solution, phosphomolybdic acid and/or scrutinised under 254 nm UV light. Column chromatography was performed using Silica 60 (35-70 microns) supplied by Fisher unless otherwise stated.

Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Avance 400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) with the appropriate deuterated solvent. Chemical shifts in ^{1}H NMR spectra are expressed as ppm downfield from TMS and in 13C NMR, are relative to internal standard, and reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (*J*) are quoted in Hz and are averaged between coupling partners and rounded to the nearest 0.2 Hz. Mass spectrometry was performed using a Bruker MicroTOF-Q instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumbers being reported in cm^{-1}.

3-(2-Azido)ethyl-6-(trifluoromethoxy)benzothiazol-2-imine (6)



1. To a solution of *N*-(4-trifluoromethoxy)phenyl)ethane-1,2-diamine[1] (0.83 g, 3.75 mmol, 1.0 equiv.), K_2CO_3 (1.21 g, 8.75 mmol, 2.3 equiv.) and $CuSO_4.5H_2O$ (9 mg, 0.04 mmol, 0.001 equiv.) in 20.0 mL MeOH under an atmosphere of N_2 was added imidazole-1-sulfonyl azide hydrochloride[2] (0.94 g, 4.50 mmol, 1.2 equiv.) portion-wise. The reaction mixture was stirred at RT for 2 h and then diluted with 60.0 mL H_2O, acidified with conc. HCl and washed three times with 40.0 mL EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude orange oil. The oil was purified *via* column chromatography using 9:1 PE 40-60 °C: EtOAc to yield *N*-(2-azido)ethyl-4-(trifluoromethoxy)aniline (0.23 g, 0.93 mmol, 25 %) as a pale yellow oil; **R_f** 0.38 (9:1 PE 40-60 °C:EtOAc); **IR** ν_{max}/cm^{-1} 3411, 2102, 1613, 1515, 1250; **^{1}H NMR** (400MHz, $CDCl_3$); 7.06 (2H, d, J = 8.5 Hz, H-3 and H-5), 6.61 (2H, d, J = 7.0 Hz, H-2 and H-6), 3.55 (2H, t, J = 6.0 Hz, H-1'), 3.34 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 43.3

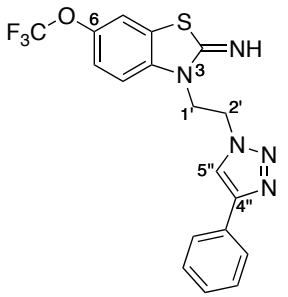
(C-2'), 50.4 (C-1'), 113.5 (C-2 and C-6), 119.4 (ArC), 122.6 (C-3 and C-5), 140.9 (Ar(OCF_3)), 145.9 (ArC); **MS** m/z $[M+H]^+$ $C_9H_{10}N_4F_3O$ requires 247.08, found 247.08.

2. To a solution of *N*-(2-azidoethyl)-4-(trifluoromethoxy)aniline (0.36 g, 1.46 mmol, 1.0 equiv.) and KSCN (1.70 g, 17.52 mmol, 12.0 equiv.) in 4.0 mL AcOH was added a solution of Br_2 (0.1 mL, 1.46 mmol, 1.0 equiv.) in 4.0 mL AcOH dropwise. This was stirred at RT for 2 h. The reaction mixture was then diluted with 24.0 mL H_2O, neutralised with 30 % NaOH solution and washed twice with EtOAc. The organic layers were combined dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude yellow oil. The crude was purified *via* column chromatography using 100 % EtOAc to yield azide **6**, 0.18 g, 0.59 mmol, 63 %) as a yellow oil; **R_f** 0.43 (100 % EtOAc); **IR** ν_{max}/cm^{-1} 2110, 1610, 1584, 1485, 1256; **^{1}H NMR** (400MHz, $CDCl_3$); 7.20 (1H, bs, H-7), 7.14 (1H, bd, J = 9.0 Hz, H-5), 7.00 (1H, d, J = 9.0 Hz, H-4), 4.14 (2H, t, J = 6.0 Hz, H-1'), 3.73 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.7 (C-1'), 48.5 (C-2'), 109.7 (C-4), 115.3 (C-7), 119.7 (C-5), 121.8 (ArC), 123.8 (ArC), 139.2 (ArC), 143.8 (Ar(OCF_3)), 161.2 (ArC); **MS** m/z $[M+H]^+$ $C_{10}H_9N_5F_3OS$ requires 304.05, found 304.05.

General Procedure for the [3 + 2] Cycloaddition of Azides and Terminal Alkynes

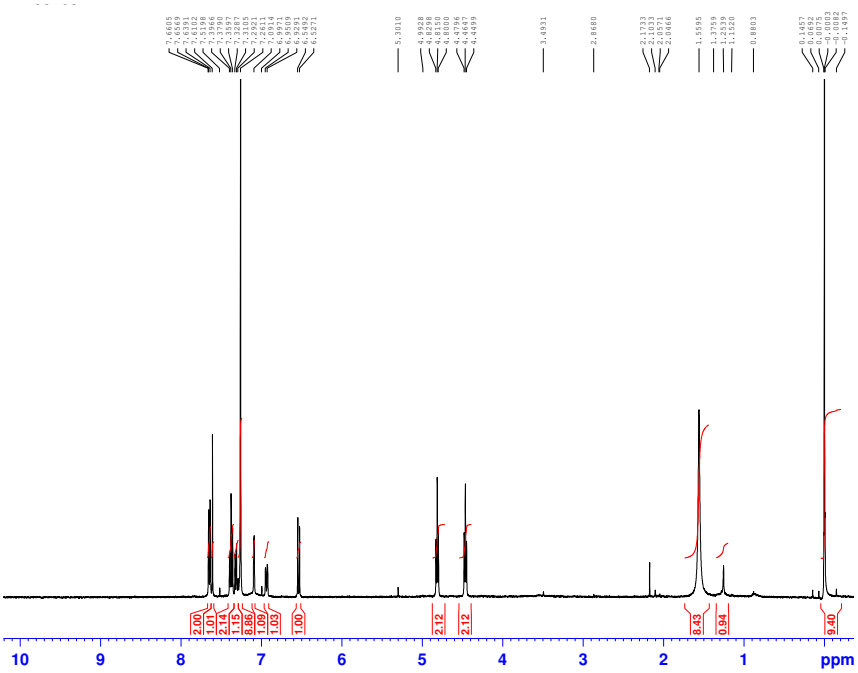
To a solution of **6** (1.0 equiv.) and alkyne (1.5 equiv.) in a 1:1 mixture of THF and H_2O heated to 20 °C was added 1M $CuSO_4$ (aq) (1.0 equiv.) and sodium ascorbate (aq., 1M, freshly prepared) (2.0 equiv.). The reaction was monitored by TLC. After consumption of azide **6** the reaction mixture was concentrated under reduced pressure to remove excess THF. This was then diluted with 8.0 mL DCM and diluted with 4.0 mL conc. NH_4OH and left to stir for 30 mins. The reaction mixture was washed twice with 8.0 mL H_2O and once with 8.0 mL brine. The organic layer was collected, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude 1,2,3-triazole, which was further purified *via* flash column chromatography in a suitable solvent system.

3-(2-(4-Phenyl-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5a

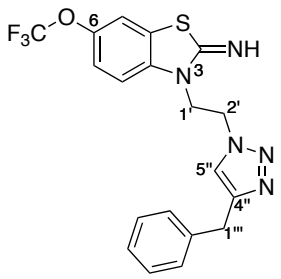


Using the general procedure; to a solution of azide **6** (0.27 g, 0.89 mmol, 1.0 equiv.) and phenylacetylene (0.2 mL, 1.32 mmol, 1.5 equiv.) in 12.0 mL H_2O and 12.0 mL THF heated to 20 °C was added 0.9 mL 1M $CuSO_4$ (aq) and 1.8 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 3 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-phenyl-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5a**, 0.14 g, 0.35 mmol, 39 %) as an off-white solid; **R_f** 0.21 (100 % EtOAc), **m.p.** 195 - 201 °C; **IR** ν_{max}/cm^{-1} 3250, 2954, 1615, 1584, 1483, 1259; **^{1}H NMR** (400MHz, $CDCl_3$); 7.65 (2H, d, J =18.5 Hz, ArH), 7.61 (1H, s, H-5''), 7.38 (2H, t, J = 7.0 Hz, ArH), 7.33 - 7.29 (1H, m, ArH), 7.09 (1H, bs, H-7), 6.94 (1H, bd, J = 8.5 Hz, H-5), 6.54 (1H, d, J = 9.0 Hz, H-4), 4.82 (2H, t, J = 6.0 Hz, H-1'), 4.47 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 43.6 (C-2'), 46.9 (C-1'), 109.0 (C-4), 115.3 (C-7), 119.8 (C-5), 120.8 (C-5''), 121.7 (ArC), 123.2 (ArC), 125.8 (ArCH), 128.3 (ArCH), 128.8 (ArCH), 130.2 (ArC), 138.56 (ArC), 143.9 (Ar(OCF_3)), 148.2 (ArC), 161.0 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{15}F_3N_5OS$ requires 406.10, found 406.09.

^{1}H NMR

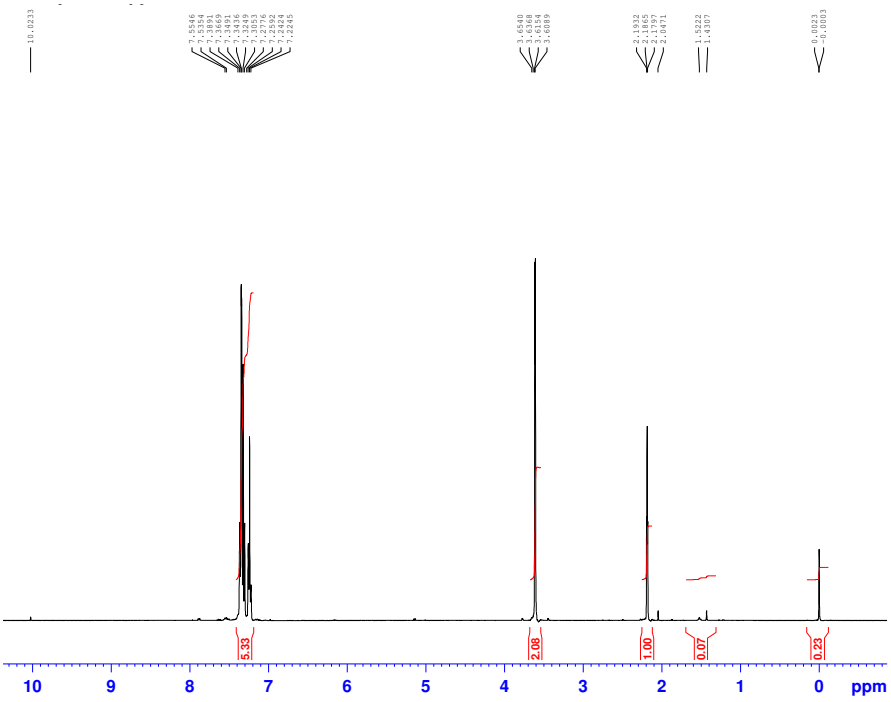


3-(2-(4-Benzyl-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5b

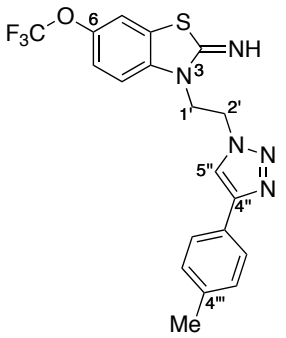


Using the general procedure; to a solution of azide **6** (0.22 g, 0.72 mmol, 1.0 equiv.) and 3-phenyl-1-propyne (0.1 mL, 1.07 mmol, 1.5 equiv.) in 8.6 mL H_2O and 8.6 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.4 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 3 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-benzyl-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5b**, 0.15 g, 0.34 mmol, 50 %) as a pale yellow solid; **R_f** 0.15 (100 % EtOAc), **m.p.** 103 - 106 °C; **IR** ν_{max}/cm^{-1} 3232, 3064, 1602, 1580, 1484, 1256; **^{1}H NMR** (400MHz, $CDCl_3$); 7.24 - 7.20 (3H, m, ArH), 7.10 (1H, bs, H-5''), 7.00 - 6.99 (2H, m, ArH), 6.96 (1H, s, H-7), 6.91 (1H, bd, J = 9.0 Hz, H-5), 6.37 (1H, d, J = 9.0 Hz, H-4), 4.71 (2H, t, J = 6.0 Hz, H-1'), 4.37 (2H, t, J = 6.0 Hz, H-2'), 3.92 (2H, s, H-1'''); **^{13}C NMR** (100MHz, $CDCl_3$); 31.0 (C-1'''), 42.8 (C-2'), 45.7 (C-1'), 107.8 (C-4), 114.0 (C-5''), 118.1 (ArC) 118.7 (C-5), 120.7 (ArC), 121.67 (ArC), 122.1 (C-7), 125.5 (ArCH), 127.5 (ArCH), 127.5 (ArCH), 137.6 (ArC), 142.7 (Ar(OCF_3)), 147.1 (ArC), 159.6 (ArC); **MS** m/z $[M+H]^+$ $C_{19}H_{17}F_3N_5OS$ requires 420.11, found 420.11.

^{1}H NMR

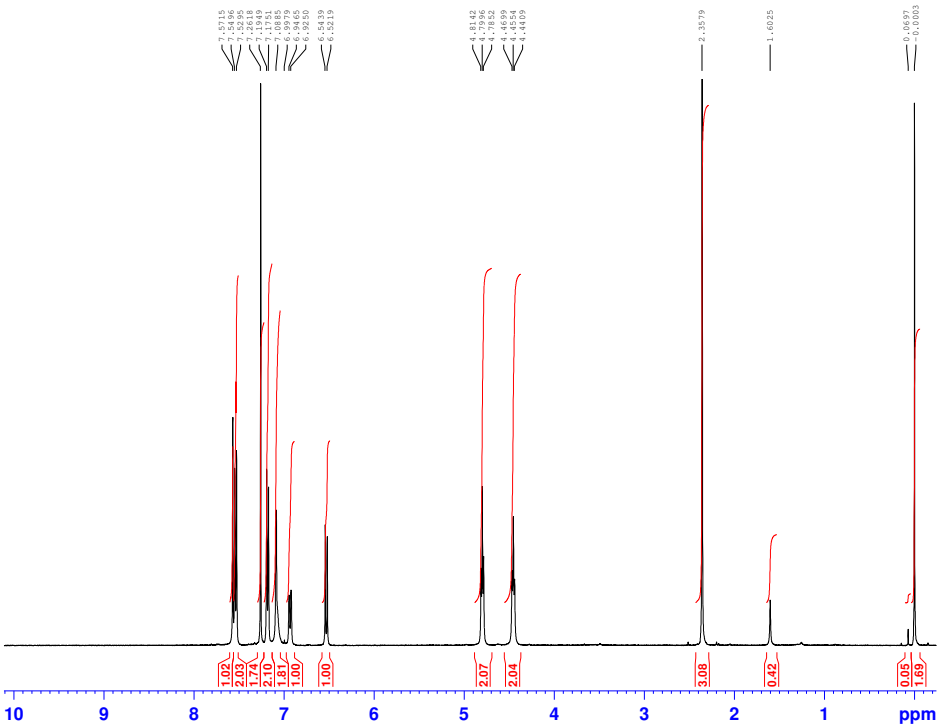


3-(2-(4-(*p*-Tolyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5c

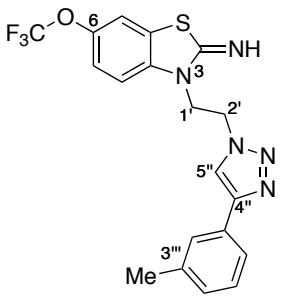


Using the general procedure; to a solution of azide **6** (0.31 g, 1.02 mmol, 1.0 equiv.) and 4-ethynyltoluene (0.1 mL, 1.07 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL $CuSO_4$ (aq) and 1.4 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(*p*-tolyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5c**, 0.17 g, 0.40 mmol, 56 %) as a pale yellow solid; **R_f** 0.27 (100 % EtOAc), **m.p.** 199 - 203 °C; **IR** ν_{max}/cm^{-1} 3273, 3014, 2943, 1626, 1586, 1479, 1386, 1252; **^{1}H NMR** (400MHz, $CDCl_3$); 7.57 (1H, s, H-5''), 7.54 (2H, d, J = 8.0 Hz, ArH), 7.19 (2H, d, J = 8.0 Hz, ArH), 7.09 (2H, bs, H-7 and NH), 6.94 (1H, d, J = 8.5 Hz, H-5), 6.53 (1H, d, J = 9.0 Hz, H-4), 4.8 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'), 2.36 (3H, s, Ar(CH_3)); **^{13}C NMR** (100MHz, $CDCl_3$); 20.2 (Ar(CH_3)), 42.6 (C-2'), 45.8 (C-1'), 108.0 (C-4), 114.2 (C-7), 118.1 (ArC), 118.8 (ArC), 119.4 (C-5), 120.6 (C-5''), 122.2 (ArC), 124.6 (ArCH), 126.3 (ArC), 128.4 (ArCH), 137.1 (ArC), 142.8 (Ar(OCF_3)), 147.2 (ArC), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{19}H_{17}F_3N_5OS$ requires 420.11, found 420.11.

^{1}H NMR

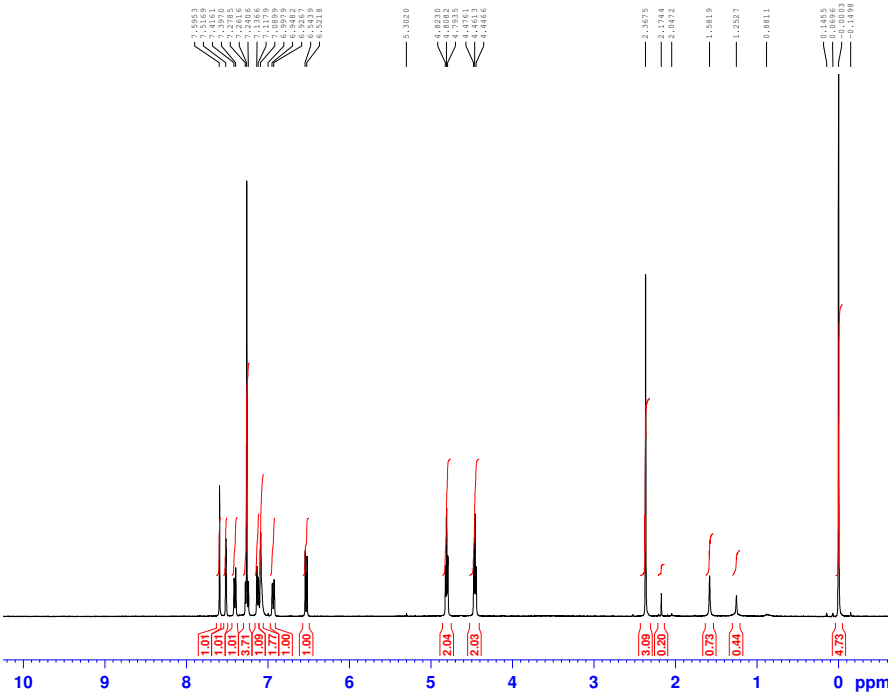


3-(2-(4-(*m*-Tolyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5d

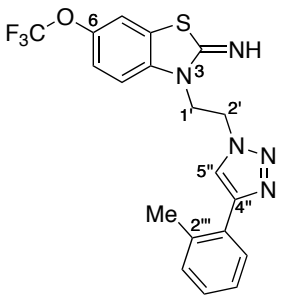


Using the general procedure; to a solution of azide **6** (0.18 g, 0.60 mmol, 1.0 equiv.) and 3-ethynyltoluene (0.1 mL, 0.90 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.6 mL 1M $CuSO_4$ (aq) and 1.2 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(*m*-tolyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5d**, 0.15 g, 0.36 mmol, 59 %) as a pale yellow solid; **R_f** (100 % EtOAc), **m.p.** 178 - 182 °C; **IR** ν_{max}/cm^{-1} 3280, 2954, 1625, 1586, 1480, 1384, 1267; **^{1}H NMR** (400MHz, $CDCl_3$); 7.60 (1H, s, ArH), 7.52 (1H, s, H-5''), 7.41 (1H, d, J = 7.5 Hz, ArH), 7.26 (1H, appt, J = 6.5 Hz, ArH), 7.13 (1H, d, J = 7.5 Hz, ArH), 7.09 (2H, bs, H-7 and NH), 6.94 (1H, d, J = 8.5 Hz, H-5), 6.53 (1H, d, J = 9.0 Hz, H-4), 4.81 (2H, t, J = 6.0 Hz, H-1'), 4.47 (2H, t, J = 6.0 Hz, H-2'), 2.37 (3H, s, Ar(CH_3)); **^{13}C NMR** (100MHz, $CDCl_3$); 20.3 (Ar(CH_3)), 42.6 (C-2'), 46.9 (C-1'), 108.0 (C-4), 114.2 (C-7), 118.1 (ArC), 118.8 (ArC), 119.7 (C-5), 120.6 (C-5''), 122.2 (ArCH), 123.2 (ArC) 125.4 (ArCH), 127.6 (ArCH), 128.0 (ArCH), 129.0 (ArC), 137.5 (ArC), 142.8 (Ar(OCF_3)), 147.2 (ArC), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{19}H_{17}F_3N_5OS$ requires 420.11, found 420.11.

^{1}H NMR

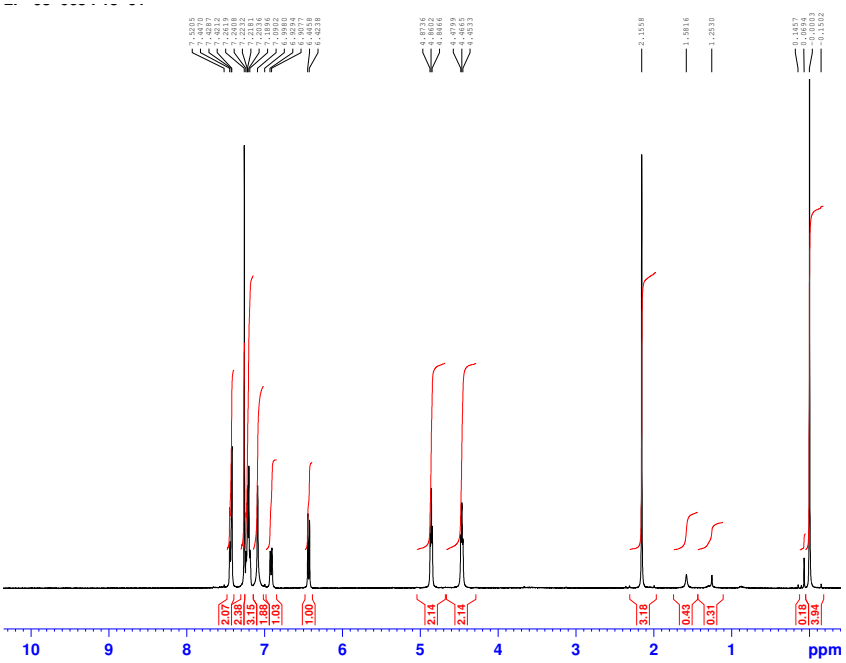


3-(2-(4-(*o*-Tolyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5e

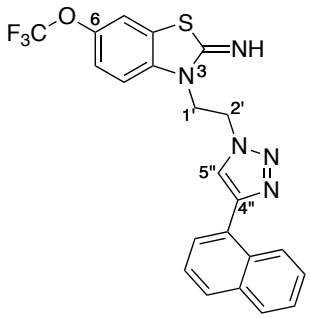


Using the general procedure; to a solution of azide **6** (0.22 g, 0.73 mmol, 1.0 equiv.) and 2-ethynyltoluene (0.1 mL, 1.09 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ and 1.5 mL freshly prepared 1M sodium ascorbate dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(*o*-tolyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5e**, 0.11 g, 0.27 mmol, 37 %) as an off-white solid; $\mathbf{R_f}$ 0.15 (100 % EtOAc), **m.p.** 165 - 170 °C; **IR** ν_{max}/cm^{-1} 3227, 3077, 2960, 1601, 1581, 1484, 1382, 1260; **^{1}H NMR** (400MHz, $CDCl_3$); 7.45 - 7.42 (2H, m, ArH and H-5''), 7.24 - 7.19 (3H, m, ArH), 7.09 (2H, bs, H -7 and NH), 6.92 (1H, d, J = 8.5 Hz, H-5), 6.44 (1H, d, J = 9.0 Hz, H-4), 4.86 (2H, t, J = 5.5 Hz, H-1'), 4.47 (2H, t, H-2', J = 5.5 Hz), 2.16 (3H, s, Ar(CH_3)); **^{13}C NMR** (100MHz, $CDCl_3$); 19.6 (Ar(CH_3)), 42.9 (C-2'), 45.9 (C-1'), 107.8 (C-4), 114.2 (C-7), 118.07 (ArC), 118.9 (C-5), 120.6 (ArC), 121.9 (C-5''), 122.1 (ArC), 125.0 (ArCH), 127.3 (ArCH), 128.0 (ArCH), 128.5 (ArC), 129.6 (ArCH), 134.6 (ArC), 137.66 (ArC), 142.8 (Ar(OCF_3)), 146.4 (ArC); **MS** m/z $[M+H]^+$ $C_{19}H_{17}F_3N_5OS$ requires 420.11, found 420.11.

^{1}H NMR

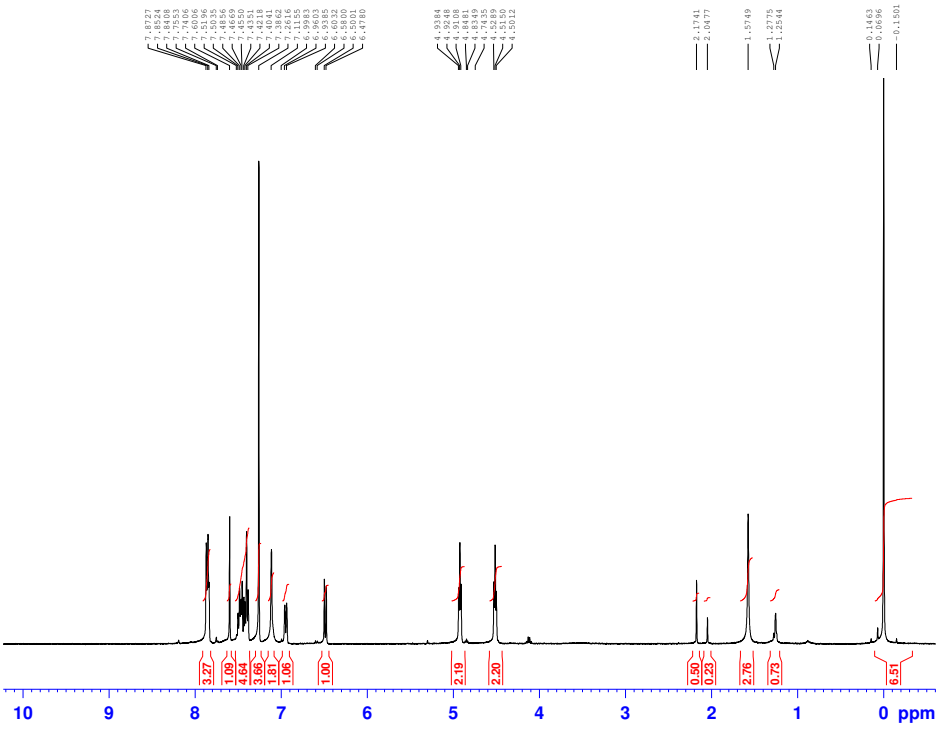


3-(2-(4-(Napthalen-1-yl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5f

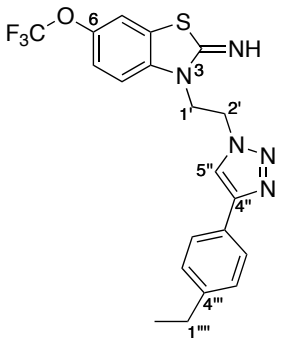


Using the general procedure; to a solution of azide **6** (0.17 g, 0.55 mmol, 1.0 equiv.) and 1-ethynylnapthalene (0.1 mL, 0.83 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.6 mL 1M $CuSO_4$ (aq) and 1.1 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(napthalen-1-yl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5f**, 0.15 g, 0.34 mmol, 61 %) as a red solid; **R_f** 0.20 (100 % EtOAc), **m.p.** 161 - 163 °C; **IR** ν_{max}/cm^{-1} 3273, 3014, 1632, 1582, 1481, 1254; **^{1}H NMR** (400MHz, $CDCl_3$); 7.87 - 7.84 (3H, m, ArH), 7.60 (1H, s, H-5''), 7.52 - 7.39 (4H, m, ArH), 7.12 (1H, s, H-7), 6.95 (1H, d, J = 8.5 Hz, H-5), 6.49 (1H, d, J = 9.0 Hz, H-4), 4.93 (2H, t, J = 5.5 Hz, H-1'), 4.52 (2H, t, J = 5.5 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.9 (C-2'), 46.0 (C-1'), 107.8 (C-4), 114.2 (C-7), 118.8 (C-4), 120.6 (ArC), 122.2 (ArC), 122.8 (C-5''), 123.9 (ArCH), 124.2 (ArCH), 125.0 (ArCH), 125.5 (ArCH), 126.2 (ArCH), 126.6 (ArC), 127.3 (ArCH), 127.9 (ArCH), 130.0 (ArC), 132.7 (ArC), 138.6 (ArC), 142.8 (Ar(OCF_3)), 146.0 (ArC), 159.7 (ArC); **MS** m/z $[M+H]^+$ $C_{22}H_{17}F_3N_5OS$ requires 456.11, found 456.11.

^{1}H NMR

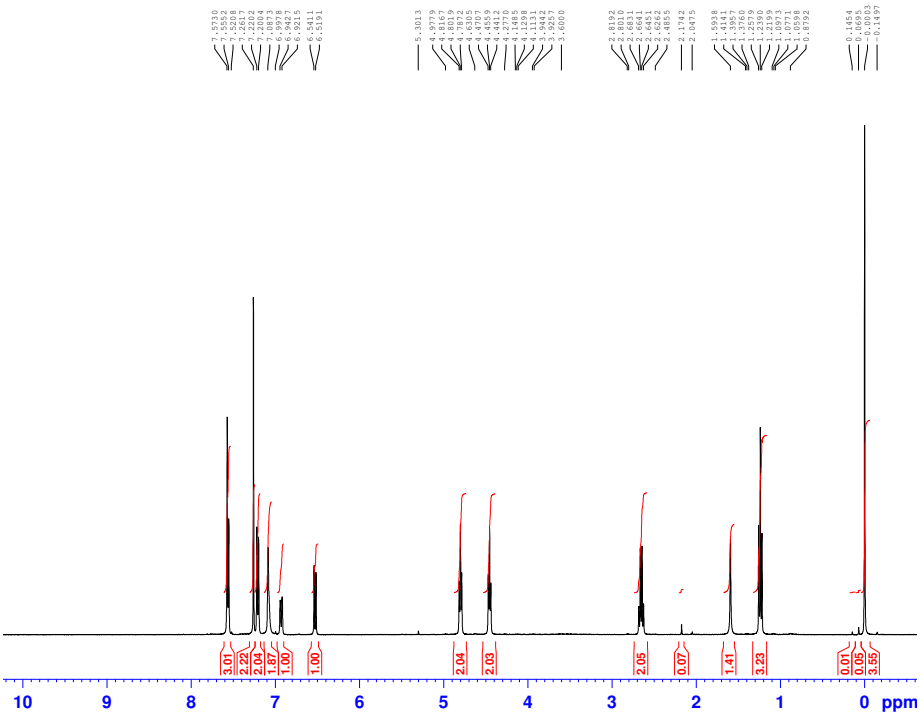


3-(2-(4-(4-Ethylphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5g

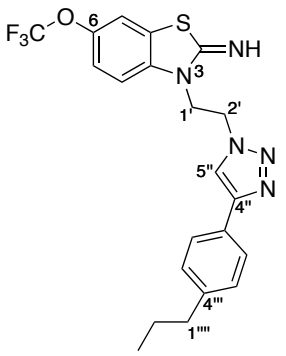


Using the general procedure; to a solution of azide **6** (0.19 g, 0.62 mmol, 1.0 equiv.) and 1-ethyl-4-ethynylbenzene (0.1 mL, 0.93 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.6 mL 1M $CuSO_4$ (aq) and 1.2 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(4-ethylphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5g**, 0.17 g, 0.40 mmol, 67 %) as an off-white solid; $\mathbf{R_f}$ 0.20 (100 % EtOAc), **m.p.** 189 - 193 °C; **IR** ν_{max}/cm^{-1} 3278, 3044, 2930, 1626, 1585, 1481, 1256; **^{1}H NMR** (400MHz, $CDCl_3$); 7.57 (3H, d, J = 7.0 Hz, H-5'' and ArH), 7.21 (2H, d, J = 8.0 Hz, ArH), 7.09 (1H, s, H-7), 6.93 (1H, d, J = 8.5 Hz, H-5), 6.53 (1H, d, J = 9.0 Hz, H-4), 4.81 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'), 2.66 (2H, q, J = 7.5 Hz, H-1''''), 1.24 (3H, t, J = 7.5 Hz, H-2''''); **^{13}C NMR** (100MHz, $CDCl_3$); 14.5 (C-2''''), 27.6 (C-1''''), 42.6 (C-2'), 45.8 (C-1'), 108.0 (C-7), 114.2 (C-4), 118.8 (C-5), 119.5 (C-5''), 120.6 (ArC), 122.2 (ArC), 124.7 (ArCH), 126.5 (ArC), 127.3 (ArCH), 137.6 (ArC), 142.8 (Ar(OCF_3)), 143.5 (ArC), 147.2 (ArC), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{20}H_{19}F_3N_5OS$ requires 434.13, found 434.12.

^{1}H NMR

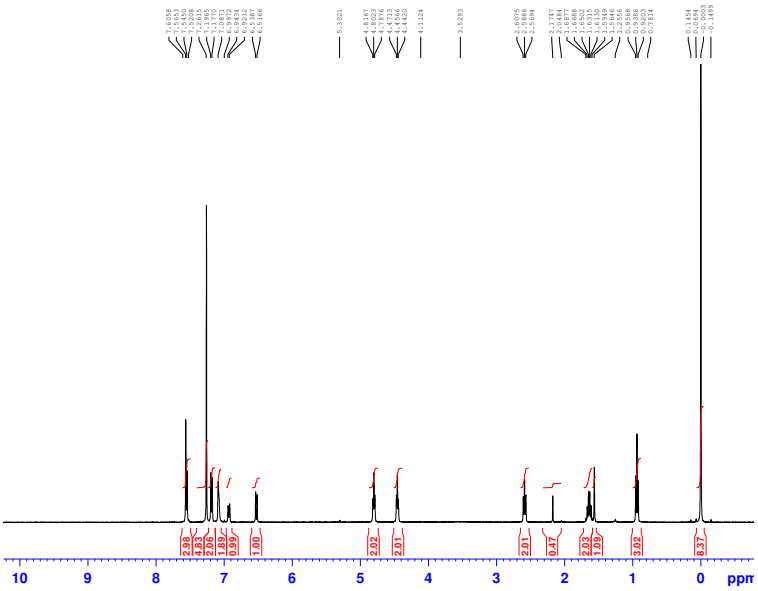


3-(2-(4-(4-Propylphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5h

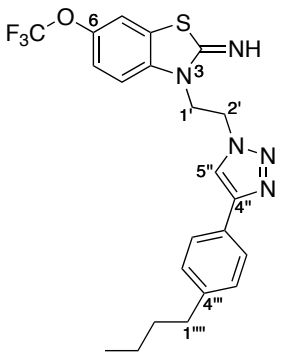


Using the general procedure; to a solution of azide **6** (0.18 g, 0.56 mmol, 1.0 equiv.) and 1-ethynyl-4-propylbenzene (0.1 mL, 0.87 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.6 mL 1M $CuSO_4$ (aq) and 1.2 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(4-propylphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5h**, 0.19 g, 0.42 mmol, 75 %) as an off-white solid; **R_f** 0.23 (100 % EtOAc), **m.p.** 190 - 196 °C; **IR** ν_{max}/cm^{-1} 3274, 3043, 2931, 1626, 1585, 1480, 1252; **^{1}H NMR** (400MHz, $CDCl_3$); 7.59 (3H, d, J = 8.0 Hz, H-5'' and ArH), 7.19 (2H, d, J = 8.0 Hz, ArH), 7.09 (1H, s, H-7), 6.93 (1H, d, J = 9.0 Hz, H-5), 6.53 (1H, d, J = 9.0 Hz, H-4), 4.81 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'), 2.59 (2H, t, J = 7.5 Hz, H-1''''), 1.63 (2H, sext, J = 7.5 Hz, H-2''''), 0.94 (3H, t, J = 7.5 Hz, H-3''''); **^{13}C NMR** (100MHz, $CDCl_3$); 12.7 (C-3''''), 23.4 (C-2''''), 36.8 (C-1''''), 42.6 (C-2'), 45.8 (C-1'), 108.0 (C-4), 114.2 (C-7), 118.8 (C-5), 119.5 (C-5''), 120.6 (ArC), 122.2 (ArC), 124.6 (ArCH), 126.6 (ArC), 127.8 (ArCH), 137.6 (ArC), 141.9 (ArC), 142.8 (Ar(OCF_3)), 147.2 (ArC), 159.9 (ArC); **MS** m/z $[M+H]^+$ $C_{21}H_{21}F_3N_5OS$ requires 448,14, found 448.14.

^{1}H NMR

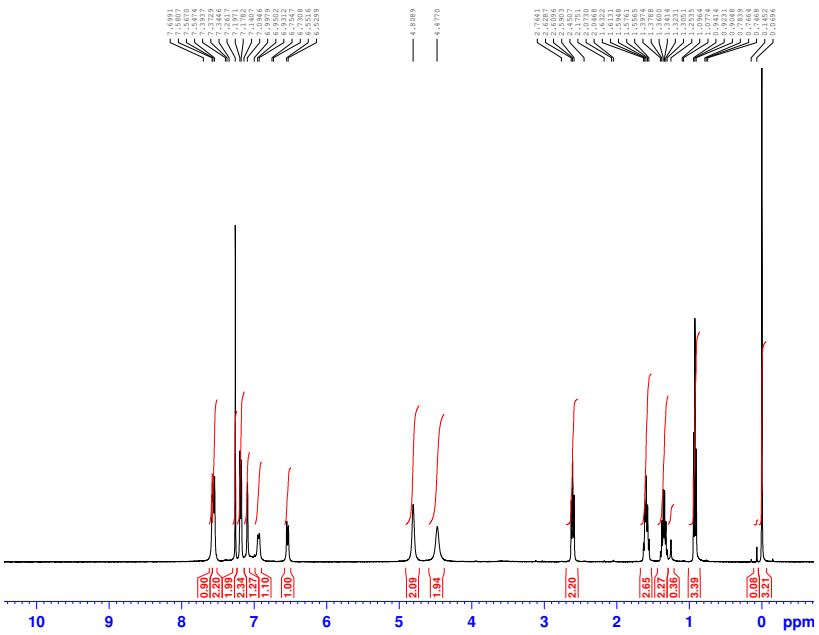


3-(2-(4-(4-Butylphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5i

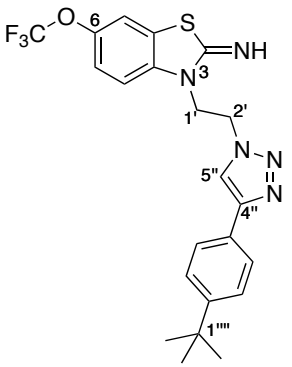


Using the general procedure; to a solution of azide **6** (0.15 g, 0.49 mmol, 1.0 equiv.) and 1-butyl-4-ethynylbenzene (0.1 mL, 0.74 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 1.0 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(4-butylphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5i**, 0.16 g, 0.35 mmol, 72 %) as a pale yellow solid; **R_f** 0.21 (100 % EtOAc), **m.p.** 183 - 186 °C; **IR** ν_{max}/cm^{-1} 3230, 3048, 2967, 1581, 1484, 1257; **^{1}H NMR** (400MHz, $CDCl_3$); 7.58 (1H, s, H-5''), 7.56 (2H, d, J = 7.5 Hz, ArH), 7.19 (2H, d, J = 7.5 Hz, ArH), 7.09 (1H, s, H-7), 6.94 (1H, d, J = 7.5 Hz, H-5), 6.54 (1H, d, J = 8.5 Hz, H-4), 4.81 (2H, bs, H-1'), 4.48 (2H, bs, H-2'), 2.61 (2H, t, J = 7.5 Hz, H-1''''), 1.60 (2H, quin, J = 7.5 Hz, H-2''''), 1.36 (2H, sext, J = 7.5 Hz, H-3''''), 0.92 (3H, t, J = 7.5 Hz, H-4''''); **^{13}C NMR** (100MHz, $CDCl_3$); 12.9 (C-4''''), 21.3 (C-3''''), 32.5 (C-2''''), 34.4 (C-1''''), 42.6 (C-2'), 45.8 (C-1'), 108.0 (C-4), 114.2 (C-7), 118.8 (C-5), 119.5 (C-5''), 120.6 (ArC), 122.2 (ArC), 124.6 (ArCH), 126.5 (ArC), 127.8 (ArCH), 137.6 (ArC), 142.2 (ArC), 142.8 (Ar(OCF_3)), 147.3 (ArC), 160.3 (ArC); **MS** m/z $[M+H]^+$ $C_{22}H_{23}F_3N_5OS$ requires 462.16, found 462.16.

^{1}H NMR

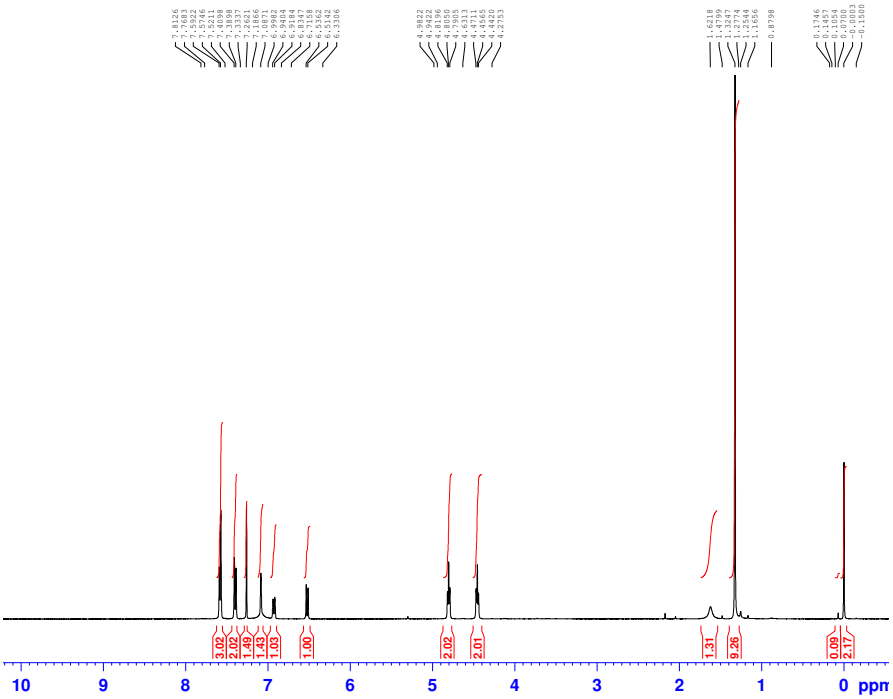


3-(2-(4-(4-(*tert*-Butyl)phenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5j

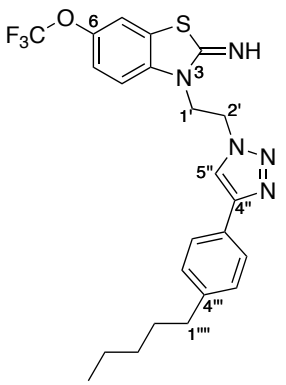


Using the general procedure; to a solution of azide **6** (0.21 g, 0.68 mmol, 1.0 equiv.) and 4-*tert*-butylphenylacetylene (0.2 mL, 1.01 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.4 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(4-(*tert*-butyl)phenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5j**, 0.23 g, 0.50 mmol, 73 %) as a pale yellow solid; $\mathbf{R_f}$ 0.24 (100 % EtOAc), **m.p.** 176 - 180 °C; **IR** ν_{max}/cm^{-1} 3321, 3007, 2953, 1604, 1583, 1483, 1256; **^{1}H NMR** (400MHz, $CDCl_3$); 7.58 (3H, d, J = 7.0 Hz, ArH and H-5''), 7.40 (2H, d, J = 8.0 Hz, ArH), 7.09 (1H, s, H -7), 6.93 (1H, d, J = 9.0 Hz, H-5), 6.53 (1H, d, J = 9.0 Hz, H-4), 4.81 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'), 1.32 (9H, s, $ArC(CH_3)_3$); **^{13}C NMR** (100MHz, $CDCl_3$); 30.2 ($ArC(CH_3)_3$), 33.6 (ArC), 42.6 (C-2'), 45.9 (C-1'), 107.8 (C-4), 114.2 (C-7), 118.8 (C-5), 119.5 (C-5''), 120.6 (ArC), 122.2 (ArC), 124.5 (ArCH), 124.7 (ArCH), 126.3 (ArC), 137.6 (ArC), 142.8 (Ar(OCF_3)), 147.1 (ArC), 150.4 (ArC), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{22}H_{23}F_3N_5OS$ requires 462.16, found 462.16.

^{1}H NMR

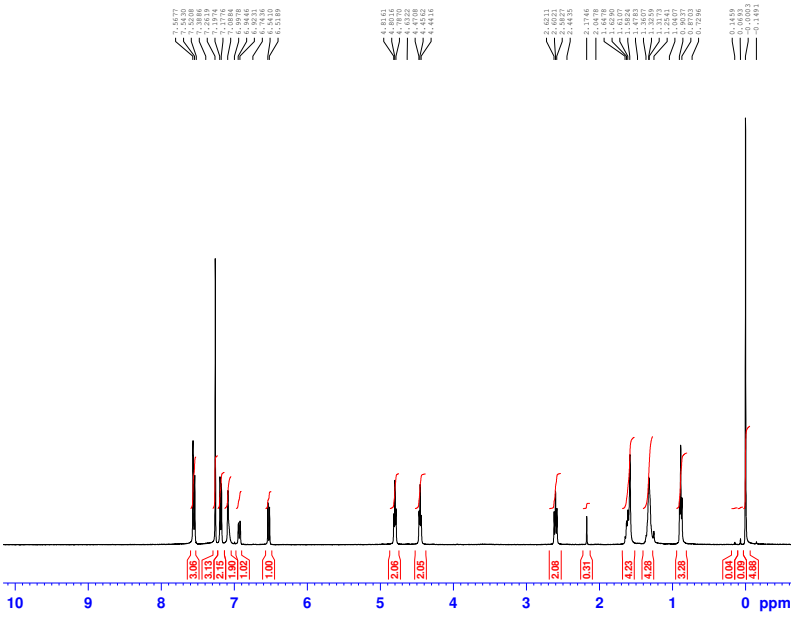


3-(2-(4-(4-Pentylphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5k

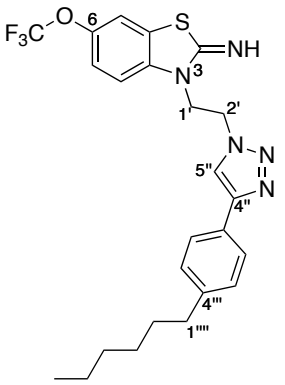


Using the general procedure; to a solution of azide **6** (0.17 g, 0.55 mmol, 1.0 equiv.) and 1-ethynyl-4-pentylbenzene (0.2 mL, 0.82 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.6 mL 1M $CuSO_4$ (aq) and 1.1 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(4-pentylphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5k**, 0.18 g, 0.38 mmol, 68 %) as a pale yellow solid; **R_f** 0.21 (100 % EtOAc), **m.p.** 184 - 187 °C; **IR** ν_{max}/cm^{-1} 3276, 3044, 2926, 1626, 1585, 1481, 1256; **^{1}H NMR** (400MHz, $CDCl_3$); 7.59 (1H, s, H-5''), 7.56 (2H, d, J = 8.0 Hz, ArH), 7.19 (2H, d, J = 8.0 Hz, ArH), 7.10 (1H, s, H-7), 6.94 (1H, d, J = 8.5 Hz, H-5), 6.55 (1H, d, J = 9.0 Hz, H-4), 4.81 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'), 2.60 (2H, t, J = 7.5 Hz, H-1''''), 1.65 - 1.58 (2H, m, H-2''''), 1.33 - 1.32 (4H, m, H-3'''' and H-4'''') 0.89 (3H, t, J = 6.5 Hz, H-5''''); **^{13}C NMR** (100MHz, $CDCl_3$); 13.2 (C-5''''), 21.5 (C-4''''), 30.0 (C-2''''), 30.4 (C-3''''), 34.7 (C-1''''), 42.6 (C-2'), 45.8 (C-1'), 108.0 (C-4), 114.2 (C-7), 118.8 (C-5), 119.4 (C-5''), 120.6 (ArC), 123.2 (ArC), 124.6 (ArCH), 126.5 (ArC), 127.8 (ArCH), 137.6 (ArC), 142.2 (ArC), 142.8 (Ar(OCF_3)), 147.2 (ArC), 159.9 (ArC); **MS** m/z $[M+H]^+$ $C_{23}H_{25}F_3N_5OS$ requires 476.18, found 476.17.

^{1}H NMR

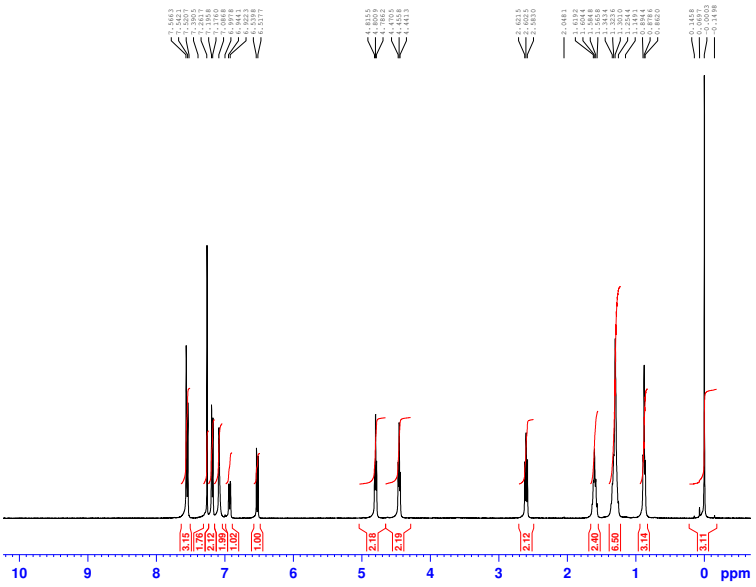


3-(2-(4-(4-Hexylphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5l

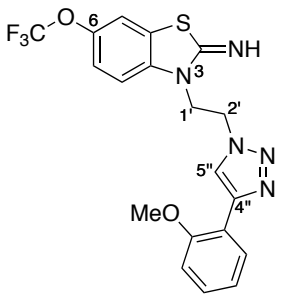


Usuiv.ing the general procedure; to a solution of azide **6** (0.18 g, 0.61 mmol, 1.0 eq) and 1-ethynyl-4-hexylbenzene (0.2 mL, 0.91 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.6 mL 1M $CuSO_4$ (aq) and 1.2 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(4-hexylphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5l**, 0.21 g, 0.44 mmol, 72 %) as a pale yellow solid; $\mathbf{R_f}$ 0.24 (100 % EtOAc), **m.p.** 175 - 180 °C; **IR** ν_{max}/cm^{-1} 3276, 3044, 2926, 1626, 1585, 1481, 1255; **^{1}H NMR** (400MHz, $CDCl_3$); 7.57 (1H, s, H-5”), 7.55 (2H, d, J = 8.0 Hz, ArH), 7.19 (2H, d, J = 8.0 Hz, ArH), 7.09 (1H, s, H-7), 6.94 (1H, d, J = 9.0 Hz, H-5), 6.53 (1H, d, J = 9.0 Hz, H-4), 4.81 (2H, d, J = 6.0 Hz, H-1’), 4.45 (2H, t, J = 6.0 Hz, H-2’), 2.60 (2H, t, J = 7.5 Hz, H-1’’’’), 1.59 (2H, quin, H-2’’’’), 1.30 (6H, m, H-3’’’’, H-4’’’’ and H-5’’’’), 0.88 (3H, t, J = 6.5 Hz, H-6’’’’); **^{13}C NMR** (100MHz, $CDCl_3$); 13.1 (C-6’’’’), 21.6 (C-5’’’’), 27.9 (C-3’’’’), 30.3 (C-2’’’’), 30.7 (C-4’’’’), 34.7 (C-1’’’’), 42.6 (C-2’), 45.8 (C-1’), 108.0 (C-4), 114.2 (C-7), 118.8 (C-5), 119.4 (C-5”), 120.6 (ArC), 122.2 (ArC), 124.6 (ArCH), 126.5 (ArC), 127.8 (ArCH), 137.6 (ArC), 142.2 (ArC), 142.8 (Ar(OCF_3)), 147.2 (ArC), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{24}H_{27}F_3N_5OS$ requires 490.19, found 490.19.

^{1}H NMR

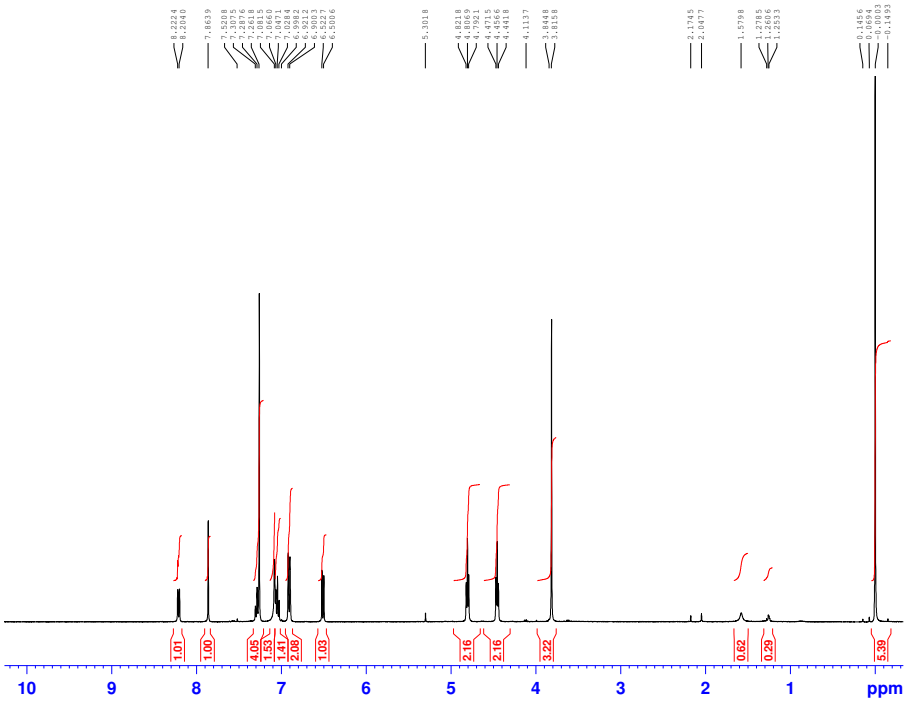


3-(2-(4-(2-Methoxyphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5m

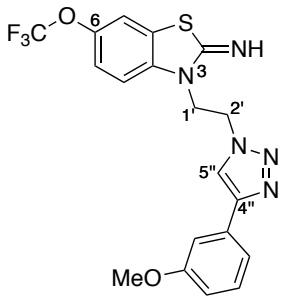


Using the general procedure; to a solution of azide **6** (0.20 g, 0.67 mmol, 1.0 equiv.) and 2-ethynylanisole (0.1 mL, 1.01 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.3 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(2-methoxyphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5m**, 0.22 g, 0.52 mmol, 77 %) as a pale yellow solid; **R_f** 0.20 (100 % EtOAc), **m.p.** 155 - 160 °C; **IR** ν_{max}/cm^{-1} 3287, 3011, 2835, 1632, 1585, 1481, 1245; **^{1}H NMR** (400MHz, $CDCl_3$); 8.21 (1H, d, J = 7.5 Hz, ArH), 7.86 (1H, s, H-5''), 7.29 (1H, appt, J = 8.0 Hz, ArH), 7.08 (1H, s, C-7), 7.05 (1H, appt, J = 7.5 Hz, ArH), 6.921 (2H, d, J = 8.5 Hz, ArH and C-5), 6.51 (1H, d, J = 9.0 Hz, C-4), 4.81 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'), 3.82 (3H, s, Ar(OCH_3)); **^{13}C NMR** (100MHz, $CDCl_3$); 42.6 (C-2'), 45.7 (C-1'), 54.2 (Ar(OCH_3)), 108.0 (C-4), 109.7 (ArCH), 114.0 (C-7), 118.0 (ArC), 118.8 (C-5), 120.0 (ArCH), 120.6 (ArC), 122.1 (ArC), 123.1 (C-5''), 126.6 (ArCH), 128.0 (ArCH), 137.7 (ArC), 142.4 (ArC), 142.7 (Ar(OCF_3)), 154.5 (ArC), 159.9 (ArC); **MS** m/z $[M+H]^+$ $C_{19}H_{17}F_3N_5O_2S$ requires 436.11, found 436.10.

^{1}H NMR

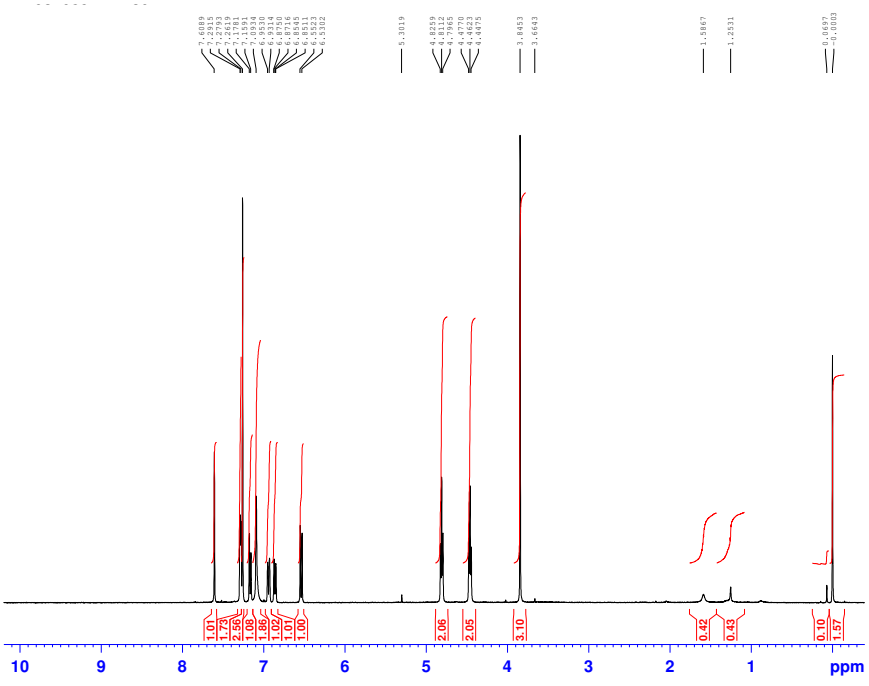


3-(2-(4-(3-Methoxyphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5n

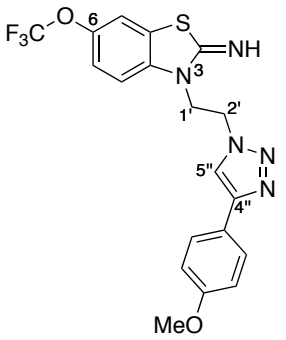


Using the general procedure; to a solution of azide **6** (0.18 g, 0.58 mmol, 1.0 equiv.) and 3-ethynylanisole (0.1 mL, 0.87 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.6 mL 1M $CuSO_4$ (aq) and 1.2 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(3-methoxyphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5n**, 0.17 g, 0.39 mmol, 67 %) as an off white solid; **R_f** 0.18 (100 % EtOAc), **m.p.** 170 - 174 °C; **IR** ν_{max}/cm^{-1} 3253, 3097, 2835, 1606, 1584, 1485, 1258; **^{1}H NMR** (400MHz, $CDCl_3$); 7.61 (1H, s, H-5''), 7.28 (2H, d, J = 5.0 Hz, ArH), 7.17 (1H, d, J = 7.5 Hz, ArH), 7.09 (1H, s, C-7), 6.94 (1H, d, J = 8.5 Hz, C-5), 6.86 (1H, d, J = 7.0 Hz, ArH), 6.54 (1H, d, J = 9.0 Hz, C-4), 4.82 (2H, t, J = 6.0 Hz, H-1'), 4.47 (2H, t, J = 6.0 Hz, H-2'), 3.85 (3H, s, Ar(OCH_3)); **^{13}C NMR** (100MHz, $CDCl_3$); 42.5 (C-2'), 45.9 (C-1'), 54.3 (Ar(OCH_3)), 108.0 (C-4), 109.8 (ArCH), 113.3 (ArCH), 114.2 (C-7), 117.1 (ArCH), 118.1 (ArC), 118.8 (C-5), 120.0 (C-5''), 120.6 (ArC), 122.2 (ArC), 128.8 (ArCH), 130.4 (ArC), 137.5 (ArC), 142.8 (Ar(OCF_3)) 147.0 (ArC), 158.9 (ArC); **MS** m/z $[M+H]^+$ $C_{19}H_{17}F_3N_5O_2S$ requires 436.11, found 436.11.

^{1}H NMR

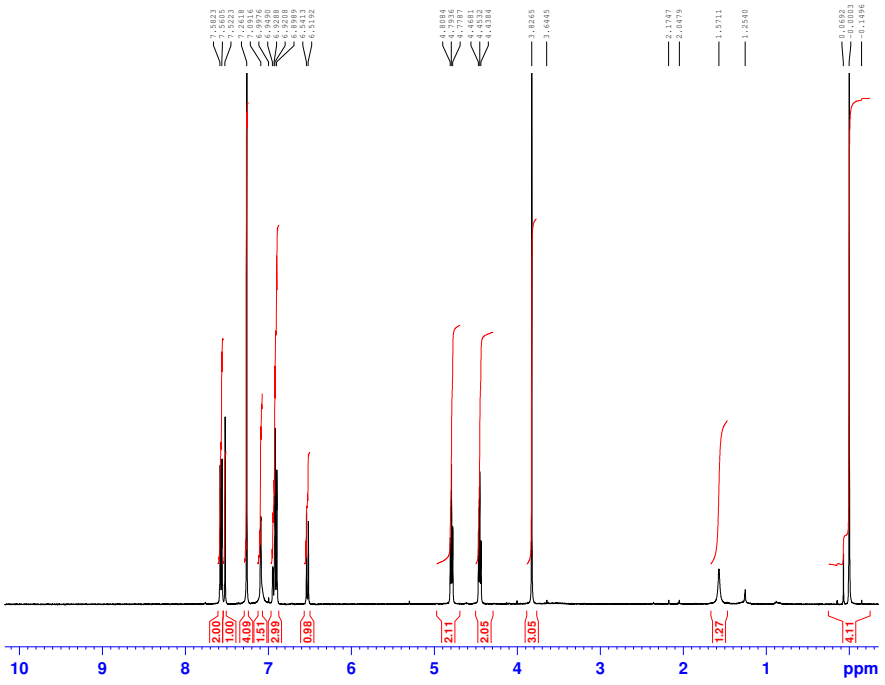


3-(2-(4-(4-Methoxyphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5o

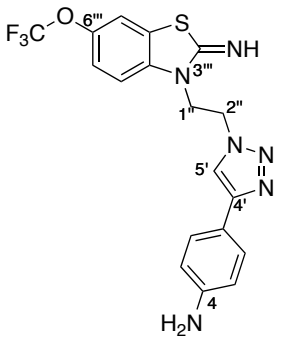


Using the general procedure; to a solution of azide **6** (0.14 g, 0.46 mmol, 1.0 equiv.) and 4-ethynylanisole (0.1 mL, 0.69 mmol, 1.5 equiv.) in 5.0 mL H_2O and 5.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 0.9 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(4-methoxyphenyl)-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5o**, 0.09 g, 0.21 mmol, 47 %) an off white solid; **R_f** 0.21 (100 % EtOAc), **m.p.** 187 - 197 °C; **IR** ν_{max}/cm^{-1} 3262, 3029, 2835, 1619, 1584, 1485, 1265; **^{1}H NMR** (400MHz, $CDCl_3$); 7.57 (2H, d, J = 9.0 Hz, ArH), 7.52 (1H, s, H-5''), 7.09 (1H, s, H-7), 6.94 (1H, d, J = 8.0 Hz, H-5), 6.91 (2H, d, J = 9.0 Hz, ArH), 6.53 (1H, d, J = 9.0 Hz, H-4), 4.80 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'), 3.83 (3H, s, Ar(OCH_3)); **^{13}C NMR** (100MHz, $CDCl_3$); 42.6 (C-2'), 45.8 (C-1'), 54.3 (Ar(OCH_3)), 108.0 (C-4), 113.2 (ArCH), 114.2 (C-7), 118.1 (ArC), 118.8 (C-5), 119.0 (C-5''), 121.8 (ArC), 122.2 (ArC), 126.0 (ArCH), 137.6 (ArC), 142.8 (Ar(OCF_3)), 147.0 (ArC), 158.6 (ArC), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{19}H_{17}F_3N_5O_2S$ requires 436.11, found 436.10.

^{1}H NMR

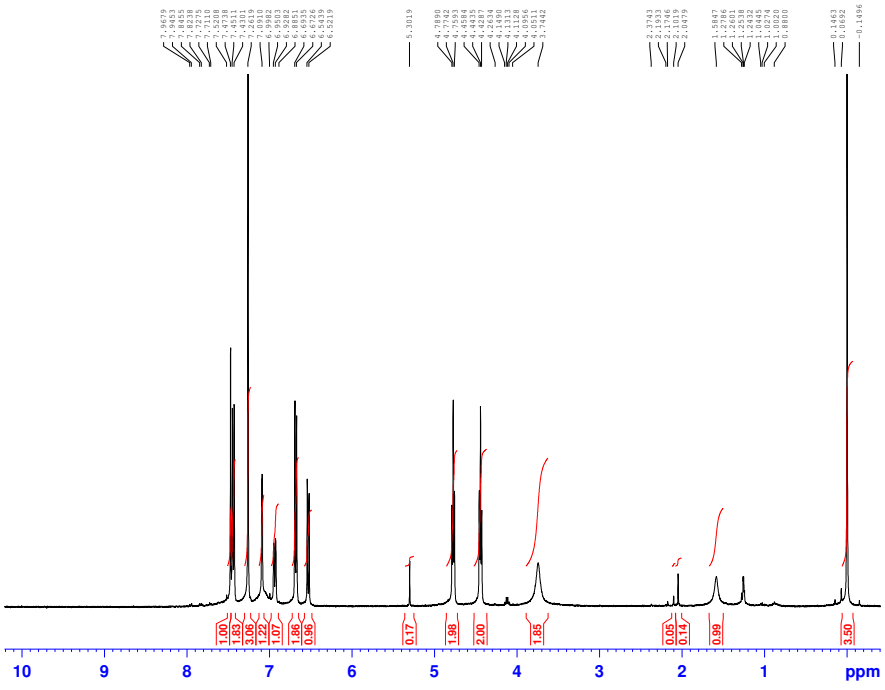


4-(1-(2-(2-Imino-6-trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl)aniline 5p

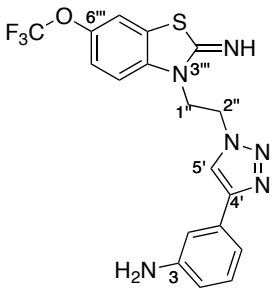


Using the general procedure; to a solution of azide **6** (0.24 g, 0.78 mmol, 1.0 equiv.) and 4-ethynylaniline (0.14 g, 1.17 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.8 mL 1M $CuSO_4$ (aq) and 1.6 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 4-(1-(2-(2-imino-6-trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl)aniline (**5p**, 0.09 g, 0.21 mmol, 27 %) as a pale yellow solid; $\mathbf{R_f}$ 0.10 (100 % EtOAc), **m.p.** 196 - 200 °C; **IR** ν_{max}/cm^{-1} 3373, 3318, 3028, 1609, 1585, 1484, 1252; ^{1}**H NMR** (400MHz, $CDCl_3$); 7.47 (1H, s, H-5'), 7.44 (2H, d, J = 8.5 Hz, ArH), 7.09 (1H, s, H-7'''), 6.94 (1H, d, J = 9.0 Hz, H-5''') 6.68 (2H, d, J = 8.5 Hz, ArH), 6.53 (1H, d, J = 9.0 Hz, H-4'''), 4.78 (2H, t, J = 6.0 Hz, H-1''), 4.45 (2H, t, J = 6.0 Hz, H-2''), 3.74 (2H, bs, Ar(NH_2)); ^{13}**C NMR** (100MHz, $CDCl_3$); 43.6 (C-2''), 46.8 (C-1''), 109.1 (C-4'''), 115.2 (ArCH and C-7'''), 119.6 (C-5'), 119.9 (C-5'''), 120.6 (ArC), 121.7 (ArC), 123.2 (ArC), 127.0 (ArCH), 138.6 (ArC), 143.8 (Ar(OCF_3)), 146.6 (ArC), 148.5 (ArC), 160.9 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{16}F_3N_6OS$ requires 421.11, found 421.11.

^{1}H NMR

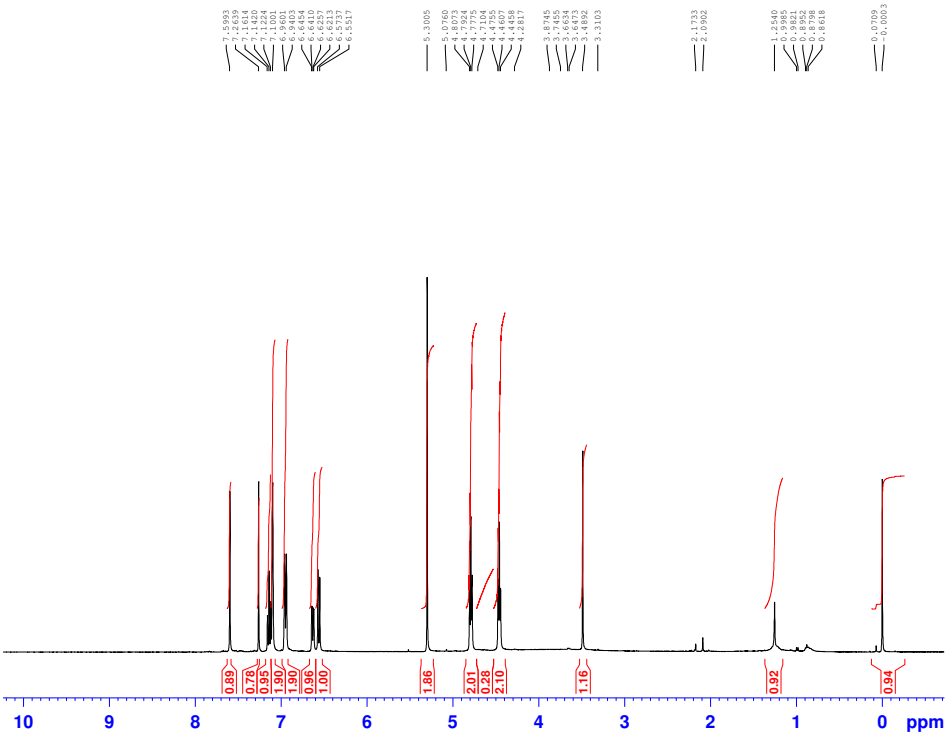


3-(1-(2-(2-Imino-6-trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl)aniline 5q

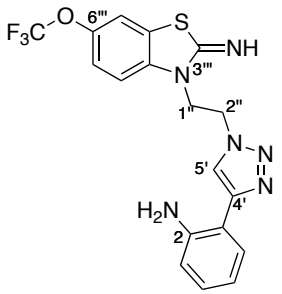


Using the general procedure; to a solution of azide **6** (0.25 g, 0.82 mmol, 1.0 equiv.) and 3-ethynylaniline (0.1 mL, 1.23 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.8 mL 1M $CuSO_4$ (aq) and 1.6 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(1-(2-(2-imino-6-trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl)aniline (**5q**, 0.15 g, 0.37 mmol, 45 %) as a pale yellow solid; $\mathbf{R_f}$ 0.10 (100 % EtOAc), **m.p.** 196 - 199 °C; **IR** ν_{max}/cm^{-1} 3461, 3295, 3036, 1620, 1586, 1481, 1262; **^{1}H NMR** (400MHz, $CDCl_3$); 7.60 (1H, s, H-5'), 7.14 (1H, t, J = 7.5 Hz, ArH), 7.10 (2H, s, H-7''' and ArH), 6.95 (2H, d, J = 8.0 Hz, H-5''' and ArH), 6.64 (1H, dd, J = 1.5 Hz and 8.0 Hz, ArH), 6.56 (1H, d, J = 9.0 Hz, H-4'''), 5.30 (2H, s. Ar(NH_2)), 4.80 (2H, t, J = 6.0 Hz, H-1''), 4.47 (2H, t, J = 6.0 Hz, H-2''); **^{13}C NMR** (100MHz, $CDCl_3$); 42.5 (C-2''), 45.8 (C-1''), 108.0 (C-4'''), 111.2 (ArCH), 114.0 (ArCH), 114.2 (C-7'''), 115.0 (ArCH), 118.8 (C-5'''), 119.8 (C-5'), 120.6 (ArC), 122.2 (ArC), 128.7 (ArCH), 130.1 (ArC), 137.5 (ArC), 142.8 (Ar(OCF_3)), 145.8 (ArC), 147.2 (ArC), 160.0 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{16}F_3N_6OS$ requires 421.11, found 421.11.

^{1}H NMR

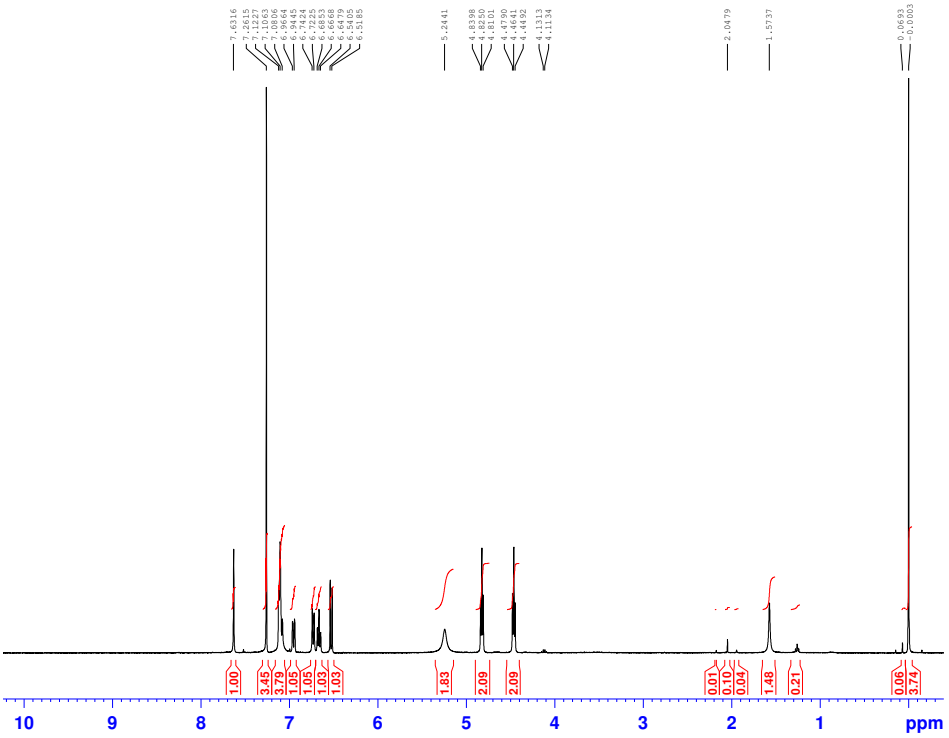


2-(1-(2-(2-Imino-6-trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl)aniline 5r

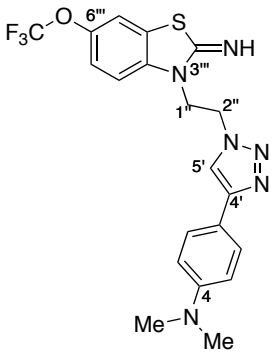


Using the general procedure; to a solution of azide **6** (0.20 g, 0.65 mmol, 1.0 equiv.) and 2-ethynylaniline (0.1 mL, 0.97 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.3 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 2-(1-(2-(2-imino-6-trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl)aniline (**5r**, 0.13 g, 0.32 mmol, 49 %) as a pale yellow solid; $\mathbf{R_f}$ 0.20 (100 % EtOAc), **m.p.** 193 - 195 °C; **IR** ν_{max}/cm^{-1} 3345, 3278, 3029, 1610, 1585, 1484, 1255; ^{1}**H NMR** (400MHz, $CDCl_3$); 7.63 (1H, s, H-5'), 7.12 - 7.08 (3H, m, H-7''' and ArH), 6.96 (1H, d, J = 8.5 Hz, H-5'''), 6.73 (1H, d, J = 8.0 Hz, ArH), 6.67 (1H, t, J = 7.5 Hz, ArH), 6.53 (1H, d, J = 9.0 Hz, H-4'''), 5.24 (2H, bs, Ar(NH_2)), 4.83 (2H, t, J = 6.0 Hz, H-1''), 4.47 (2H, t, J = 6.0 Hz, H-2''); ^{13}**C NMR** (100MHz, $CDCl_3$); 43.5 (C-2''), 46.9 (C-1''), 108.9 (C-4'''), 113.4 (ArC), 115.3 (C-7'''), 116.6 (ArCH), 117.4 (ArCH), 119.9 (C-5'''), 121.1 (C-5'), 123.3 (ArC), 127.8 (ArCH), 129.2 (ArCH), 138.6 (ArC), 143.9 (Ar(OCF_3)), 148.7 (ArC), 154.1 (ArC), 157.9 (ArC), 160.1 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{16}F_3N_6OS$ requires 421.11, found 421.11.

^{1}H NMR

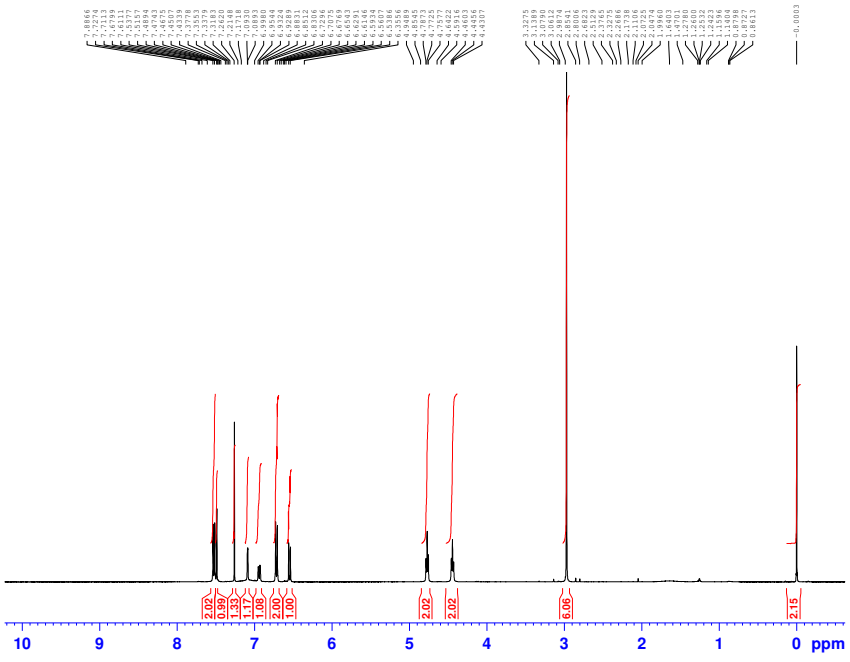


4-(1-(2-(2-Imino-6-(trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl)-*N,N*-dimethylaniline 5s

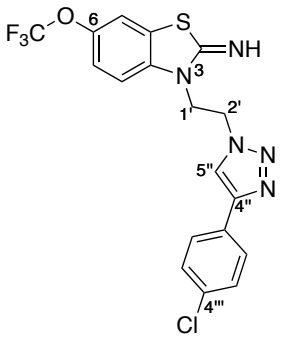


Using the general procedure; to a solution of azide **6** (0.20 g, 0.67 mmol, 1.0 equiv.) and 4-ethynyl-N,N-dimethylaniline (0.15 g, 1.01 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.3 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 4-(1-(2-(2-imino-6-(trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl)-*N,N*-dimethylaniline (**5s**, 0.17 g, 0.39 mmol, 58 %) as a pale yellow solid; $\mathbf{R_f}$ 0.17 (100 % EtOAc), **m.p.** 214 - 217 °C; **IR** ν_{max}/cm^{-1} 3246, 2945, 1614, 1584, 1483, 1251; **^{1}H NMR** (400MHz, $CDCl_3$); 7.53 (2H, d, J = 9.0 Hz, ArH), 7.49 (1H, s, H-5'), 7.09 (1H, d, J = 1.5 Hz, H-7'''), 6.94 (1H, d, J = 9.0 Hz, H-5'''), 6.72 (2H, d, J = 9.0 Hz, ArH), 6.55 (1H, d, J = 9.0 Hz, H-4'''), 4.798 (2H, t, J = 6.0 Hz, H-1''), 4.45 (2H, t, J = 6.0 Hz, H-2''), 2.99 (6H, s, $ArN(CH_3)_2$); **^{13}C NMR** (100MHz, $CDCl_3$); 40.5 ($ArN(CH_3)_2$), 43.7 (C-2''), 46.8 (C-1''), 109.1 (C-4'''), 112.4 (ArCH), 115.2 (C-7'''), 118.4 (ArC), 119.3 (C-5'), 119.9 (C-5'''), 123.2 (ArC), 126.7 (ArCH), 138.6 (ArC), 143.8 (ArC), 148.6 (ArC), 150.5 (ArC), 160.9 (ArC); **MS** m/z $[M+H]^+$ $C_{20}H_{20}F_3N_6OS$ requires 449.14, found 449.14.

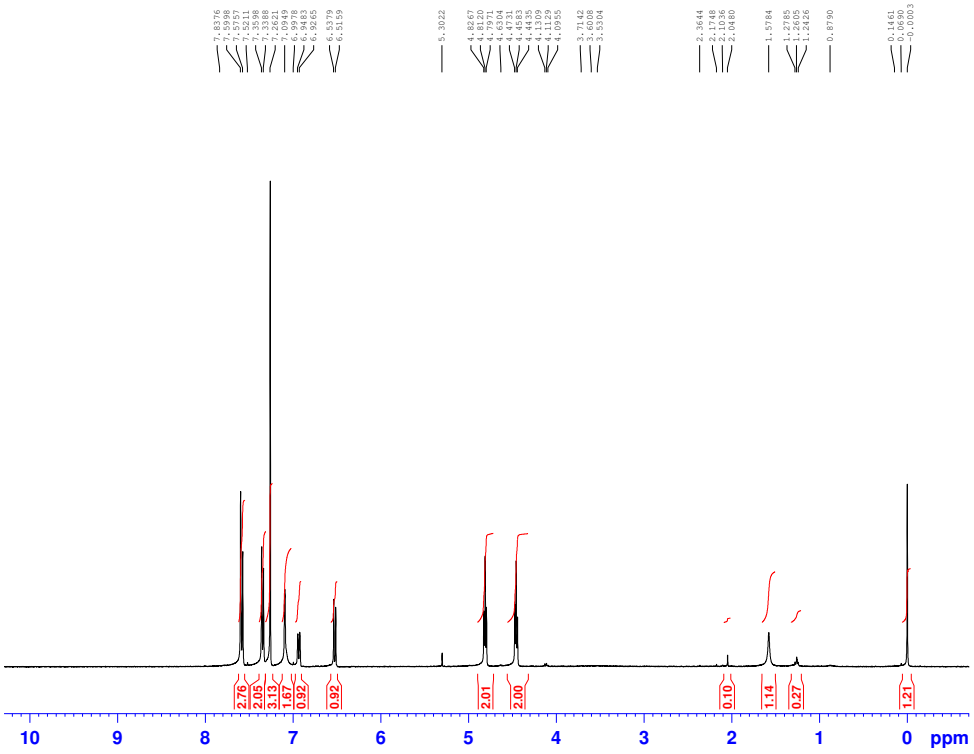
^{1}H NMR



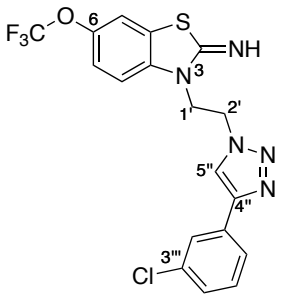
3-(2-(4-(4-Chlorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine 5t



Using the general procedure; to a solution of azide **6** (0.25 g, 0.81 mmol, 1.0 equiv.) and 1-chloro-4-ethynylbenzene (0.17 g, 1.21 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.8 mL 1M $CuSO_4$ (aq) and 1.6 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(4-chlorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine (**5t**, 0.19 g, 0.44 mmol, 55 %) as an off-white solid; **R_f** 0.18 (100 % EtOAc), **m.p.** 206 -209 °C; **IR** ν_{max}/cm^{-1} 3255, 3086, 1617, 1586, 1484, 1237, 827; **^{1}H NMR** (400MHz, $CDCl_3$); 7.60 (1H, s, H-5''), 7.58 (2H, d, J = 5.0 Hz, ArH), 7.35 (2H, d, J = 8.5 Hz, ArH), 7.09 (1H, s, H-7), 6.94 (1H, d, J = 8.5 Hz, H-5), 6.53 (1H, d, J = 9.0 Hz, H-4), 4.82 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 43.5 (C-2'), 46.9 (C-1'), 108.9 (C-4), 115.3 (C-7), 119.9 (C-5), 120.8 (C-5''), 123.2 (ArC), 127.0 (ArCH), 129.0 (ArCH), 132.9 (ArC), 134.0 (ArC), 138.5 (ArC), 143.9 (Ar(OCF_3)), 147.1 (ArC), 154.7 (ArC), 160.9 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{14}ClF_3N_5OS$ requires 440.06, found 440.05.

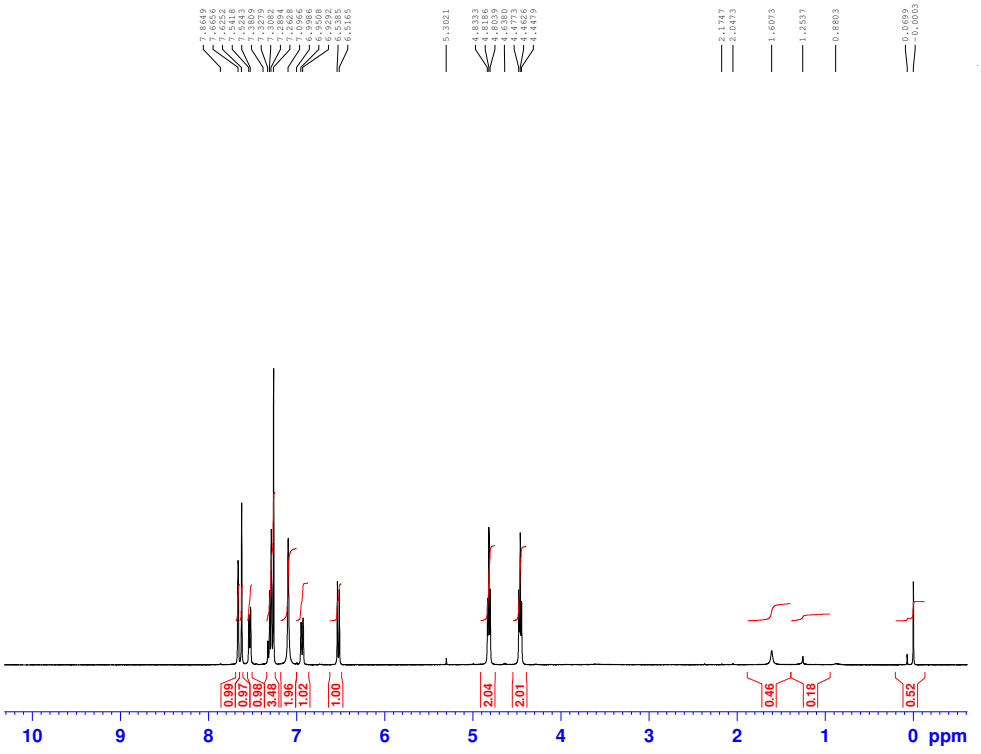


3-(2-(4-(3-Chlorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine 5u

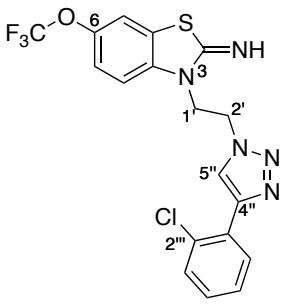


Using the general procedure; to a solution of azide **6** (0.30 g, 0.98 mmol, 1.0 equiv.) and 3-chloro-1-ethynylbenzene (0.2 mL, 1.47 mmol, 1.5 equiv.) in 15.0 mL H_2O and 15.0 mL THF heated to 20 °C was added 1.0 mL 1M $CuSO_4$ (aq) and 2.0 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(3-chlorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine (**5u**, 0.25 g, 0.57 mmol, 58 %) as an off-white solid; **R_f** 0.23 (100 % EtOAc), **m.p.** 183 - 187 °C; **IR** ν_{max}/cm^{-1} 3242, 3043, 1612, 1581, 1481, 1254, 794; **^{1}H NMR** (400MHz, $CDCl_3$); 7.67 (1H, s, ArH), 7.63 (1H, s, H-5''), 7.53 (1H, d, J = 7.0 Hz, ArH), 7.33 - 7.26 (2H, m, ArH), 7.10 (1H, s, H-7), 6.94 (1H, d, J = 8.5 Hz, H-5), 6.53 (1H, d, J = 9.0 Hz, H-4), 4.82 (2H, t, J = 6.0 Hz, H-1'), 4.47 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 43.5 (C-2'), 47.0 (C-1'), 108.9 (C-4), 115.3 (C-7), 119.9 (C-4), 121.1 (C-5''), 123.2 (ArC), 123.8 (ArCH), 125.8 (ArCH), 128.3 (ArCH), 130.1 (ArCH), 131.9 (ArC), 134.8 (ArC), 138.5 (ArC), 143.8 (Ar(OCF_3)), 146.9 (ArC), 156.6 (ArC), 160.8 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{14}ClF_3N_5OS$ requires 440.06, found 440.05.

^{1}H NMR

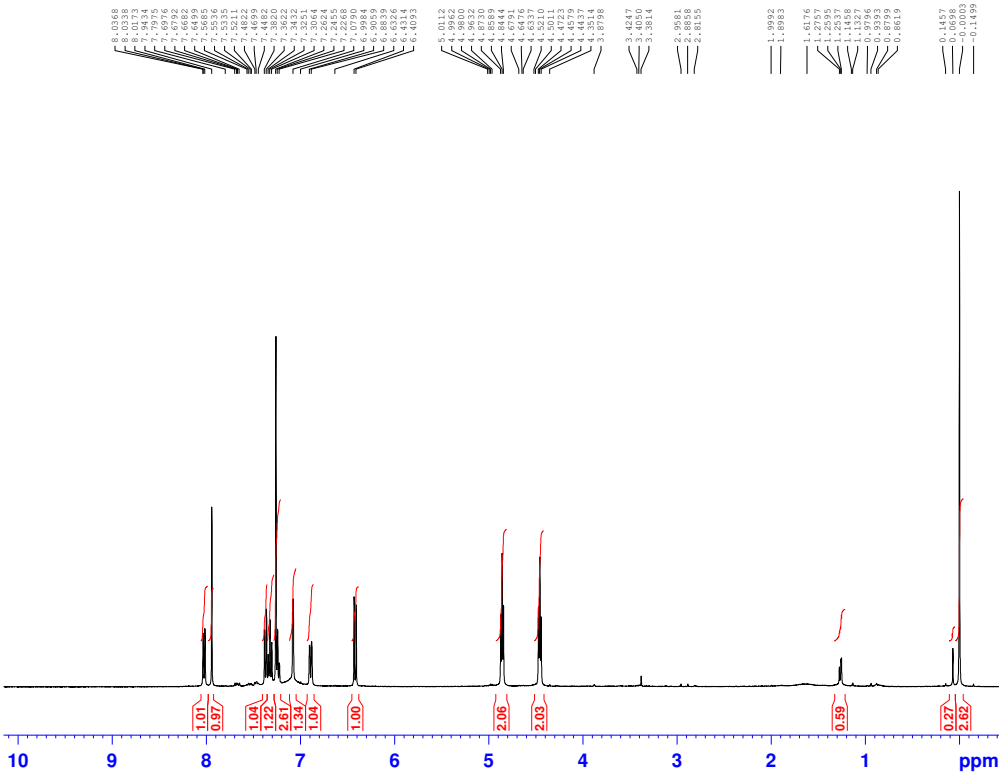


3-(2-(4-(2-Chlorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine 5v

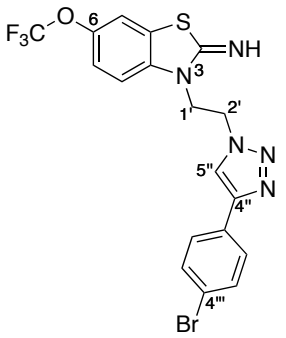


Using the general procedure; to a solution of azide **6** (0.17 g, 0.56 mmol, 1.0 equiv.) and 1-chloro-2-ethynylbenzene (0.1 mL, 0.84 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.6 mL 1M $CuSO_4$ (aq) and 1.1 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(2-chlorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine (**5v**, 0.13 g, 0.30 mmol, 53 %) as a pale yellow solid; $\mathbf{R_f}$ 0.30 (100 % EtOAc), **m.p.** 154 - 157 °C; **IR** ν_{max}/cm^{-1} 3245, 1614, 1584, 1484, 1253, 757; **^{1}H NMR** (400MHz, $CDCl_3$); 8.03 (1H, d, J = 8.0 Hz, ArH), 7.94 (1H, s, H-5''), 7.37 (1H, d, J = 8.0 Hz, ArH), 7.33 (1H, t, J = 7.0 Hz, ArH), 7.26 -7.23 (1H, m, ArH), 7.08 (1H, s H-7), 6.90 (1H, d, J = 9.0 Hz, H-5), 6.42 (1H, d, J = 9.0 Hz), 4.86 (2H, d, J = 5.5 Hz, H-1'), 4.46 (2H, d, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.6 (C-2'), 45.9 (C-1'), 107.7 (C-4), 114.2 (C-7), 118.8 (C-4), 120.6 (ArC), 122.2 (ArC), 123.3 (C-5''), 126.1 (ArCH), 127.8 (ArC), 128.1 (ArCH), 128.8 (ArCH), 129.0 (ArCH), 130.2 (ArC), 137.6 (ArC), 142.8 (Ar(OCF_3)), 143.3 (ArC), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{14}ClF_3N_5OS$ requires 440.06, found 440.05.

^{1}H NMR

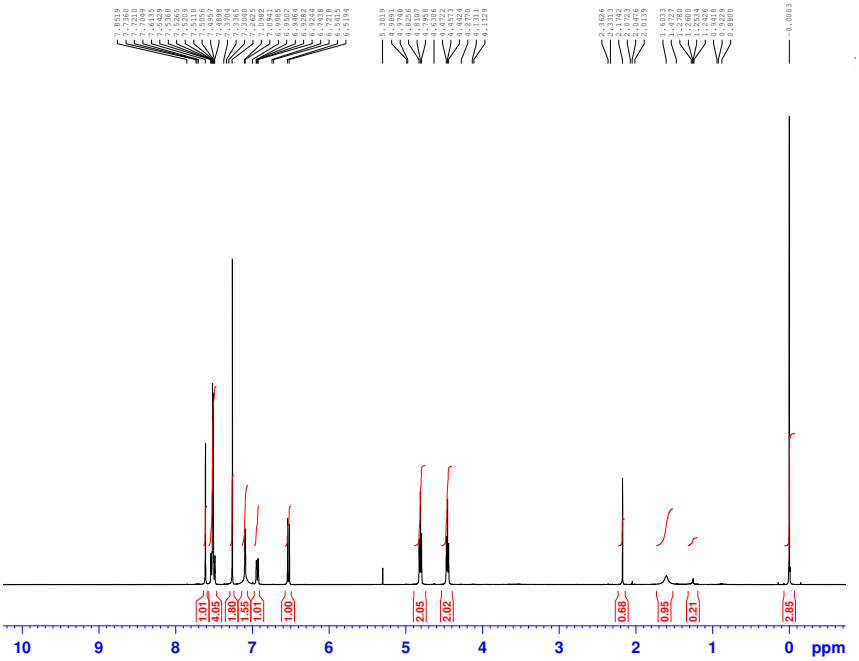


3-(2-(4-(4-Bromophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine 5w

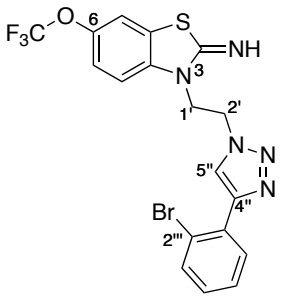


Using the general procedure; to a solution of azide **6** (0.17 g, 0.55 mmol, 1.0 equiv.) and 1-bromo-4-ethynylbenzene (0.15 g, 0.82 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.6 mL 1M $CuSO_4$ (aq) and 1.1 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(4-bromophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine (**5w**, 0.18 g, 0.38 mmol, 69 %) as an off-white solid; **R_f** 0.17 (100 % EtOAc), **m.p.** 213 - 215 °C; **IR** ν_{max}/cm^{-1} 3240, 3087, 1614, 1584, 1484, 1254, 757; **^{1}H NMR** (400MHz, $CDCl_3$); 7.61 (1H, s, H-5''), 7.54 - 7.49 (4H, m, ArH), 7.10 (1H, d, J = 1.5 Hz, H-7), 6.94 (1H, dd, J = 1.5 Hz and 9.0 Hz, H-5), 6.53 (1H, d, J = 9.0 Hz, H-4), 4.82 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-1'); **^{13}C NMR** (100MHz, $CDCl_3$); 43.5 (C-1'), 46.9 (C-2'), 108.9 (C-4), 115.3 (C-7), 119.8 (C-5), 120.9 (C-5''), 122.2 (ArC), 123.2 (ArC), 127.2 (ArCH), 129.1 (ArC), 132.0 (ArCH), 138.5 (ArC), 147.1 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{14}BrF_3N_5OS$ requires 484.01, found 484.00.

^{1}H NMR

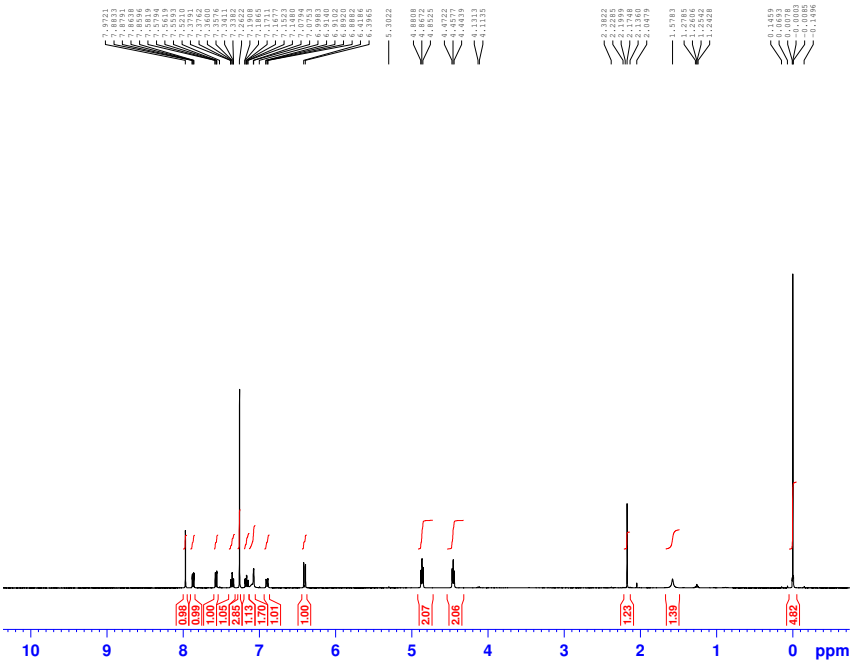


3-(2-(4-(2-Bromophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine 5x

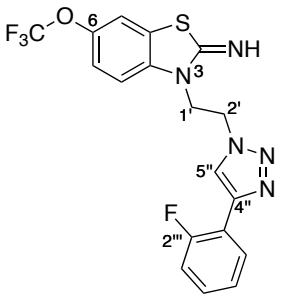


Using the general procedure; to a solution of azide **6** (0.16 g, 0.53 mmol, 1.0 equiv.) and 1-bromo-2-ethynylbenzene (0.1 mL, 0.80 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 1.1 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was left to stir at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(2-bromophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine (**5x**, 0.13 g, 0.26 mmol, 50 %) as a pale yellow solid; $\mathbf{R_f}$ 0.25 (100 % EtOAc), **m.p.** 169 - 174 °C; **IR** ν_{max}/cm^{-1} 3254, 3083, 1616, 1585, 1484, 1234; **^{1}H NMR** (400MHz, $CDCl_3$); 7.97 (1H, s, H-5''), 7.87 (1H, dd, J = 1.5 Hz and 8.0 Hz, ArH), 7.57 (1H, dd, J = 1.0 Hz and 8.0 Hz, ArH), 7.36 (1H, td, J = 1.0 Hz and 7.5 Hz, ArH), 7.17 (1H, td, J = 1.5 Hz and 8.0 Hz, ArH), 7.08 (1H, d, J = 1.5 Hz, H-7), 6.90 (1H, dd, J = 1.5 Hz and 9.0 Hz, H-5), 6.41 (1H, d, J = 9.0 Hz, H-4), 4.87 (2H, t, J = 5.5 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 43.8 (C-2'), 47.1 (C-1'), 108.8 (C-4), 115.3 (C-7), 119.9 (C-5), 121.2 (ArC), 123.2 (ArC), 124.2 (C-5''), 127.6 (ArCH), 129.5 (ArCH), 130.5 (ArCH), 133.4 (ArCH), 138.6 (ArC), 145.7 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{14}BrF_3N_5OS$ requires 484.01, found 484.00.

^{1}H NMR

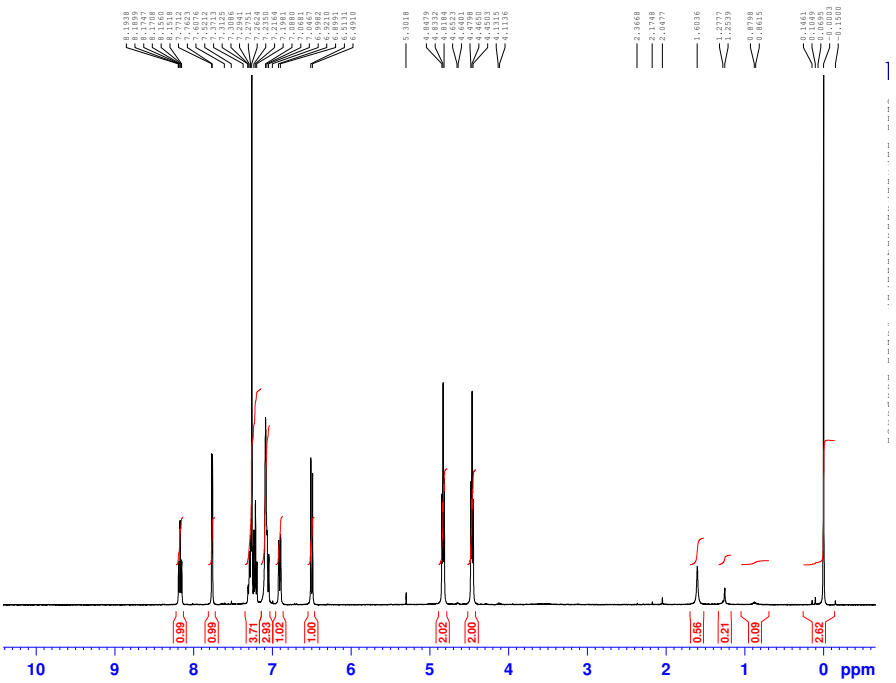


3-(2-(4-(2-Fluorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine 5y

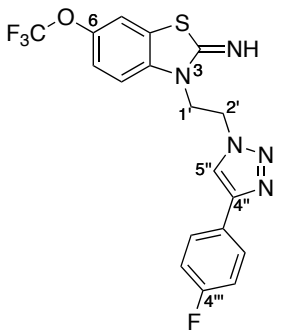


Using the general procedure; to a solution of azide **6** (0.28 g, 0.93 mmol, 1.0 equiv.) and 1-ethynyl-2-fluorobenzene (0.2 mL, 1.39 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.9 mL 1M $CuSO_4$ (aq) and 1.9 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(2-fluorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine (**5y**, 0.21 g, 0.49 mmol, 52 %) as an off-white solid; **R_f** 0.33 (100 % EtOAc), **m.p.** 172 - 175 °C; **IR** ν_{max}/cm^{-1} 3243, 3068, 2958, 1576, 1483, 1254; **^{1}H NMR** (400MHz, $CDCl_3$); 8.17 (1H, td, J = 1.5 Hz and 7.5 Hz, ArH), 7.77 (1H, d, J = 3.5 Hz, H-5''), 7.31 - 7.28 (1H, m, ArH), 7.22 (1H, t, J = 7.5 Hz, ArH), 7.09 - 7.00 (3H, m, ArH, Ar(NH), and H-7), 6.91 (1H, d, J = 8.5 Hz, H-5), 6.50 (1H, d, J = 9.0 Hz, H-4), 4.84 (2H, t, J = 6.0 Hz, H-1'), 4.47 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.5 (C-2'), 45.8 (C-1'), 107.8 (C-4), 114.2 (C-7), 114.5 (ArCH), 117.1 (ArC), 118.7 (C-5), 122.2 (ArC), 122.8 (C-5''), 123.5 (ArCH), 126.7 (ArCH), 128.4 (ArCH), 137.5 (ArC), 140.4 (ArC), 142.7 (Ar(OCF_3)), 156.8 (ArC), 159.8 (ArC), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{14}F_4N_5OS$ requires 424.09, found 424.08.

^{1}H NMR

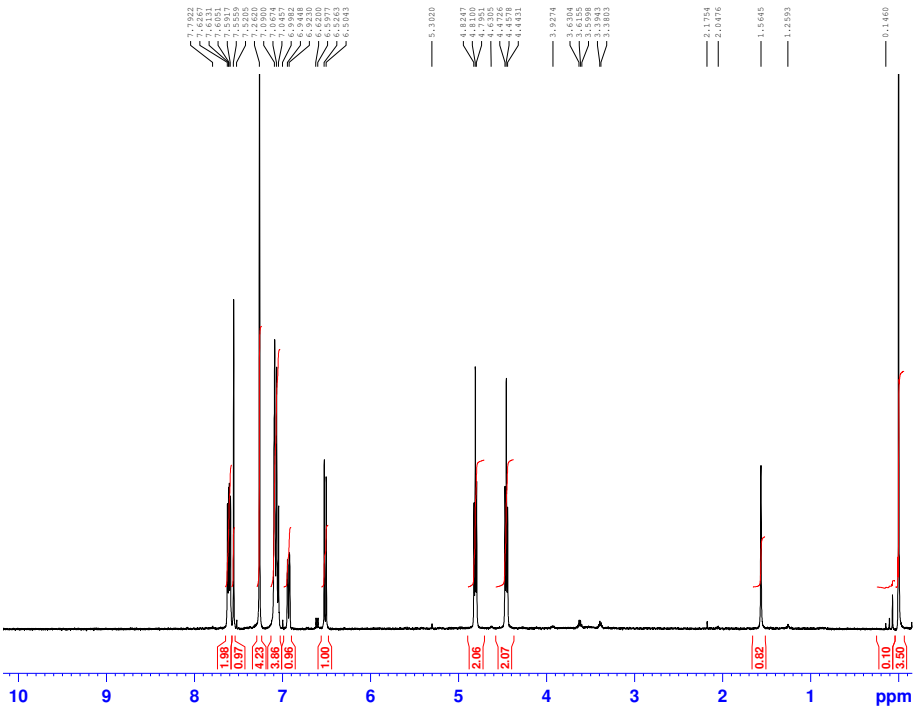


3-(2-(4-(4-Fluorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine 5z

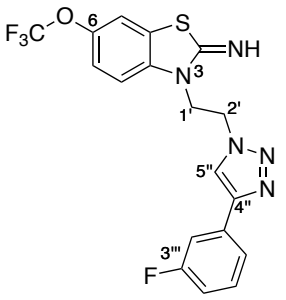


Using the general procedure; to a solution of azide **6** (0.21 g, 0.70 mmol, 1.0 equiv.) and 1-ethynyl-4-fluorobenzene (0.1 mL, 1.05 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.4 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(4-fluorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine (**5z**, 0.16 g, 0.39 mmol, 56 %) as an off-white solid; **R_f** 0.15 (100 % EtOAc), **m.p.** 193 - 197 °C; **IR** ν_{max}/cm^{-1} 3230, 3014, 1601, 1582, 1484, 1261; **^{1}H NMR** (400MHz, $CDCl_3$); 7.61 (2H, dd, J = 5.5 Hz and 8.5 Hz, ArH), 7.56 (1H, s, H-5''), 7.09 (1H, s, H-7), 7.06 (2H, appt, J = 8.5 Hz, ArH), 6.93 (1H, d, J = 8.5 Hz, H-5), 6.52 (1H, d, J = 9.0 Hz, H-4), 4.81 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.5 (C-2'), 45.9 (C-1'), 107.9 (C-4), 114.2 (C-7), 114.7 (ArCH), 114.9 (ArCH), 118.8 (C-5), 119.5 (C-5''), 122.2 (ArC), 126.4 (ArC), 126.5 (ArC), 137.5 (ArC), 142.8 (Ar(OCF_3)), 146.3 (ArC), 159.8 (ArC), 162.9 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{14}F_4N_5OS$ requires 424.09, found 424.08.

^{1}H NMR

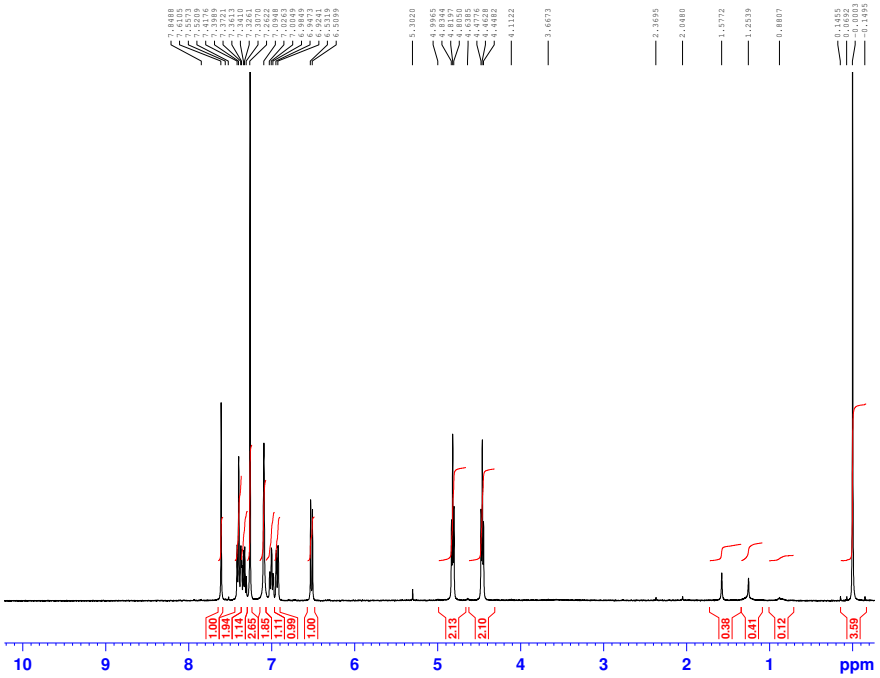


3-(2-(4-(3-Fluorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine 5aa

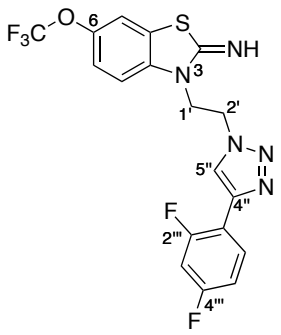


Using the general procedure; to a solution of azide **6** (0.26 g, 0.84 mmol, 1.0 equiv.) and 1-ethynyl-3-fluorobenzene (0.2 mL, 1.27 mmol, 1.5 equiv.) in 15.0 mL H_2O and 15.0 mL THF heated to 20 °C was added 0.8 mL 1M $CuSO_4$ (aq) and 1.7 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(3-fluorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine (**5aa**, 0.16 g, 0.37 mmol, 44 %) as an off-white solid; **R_f** 0.19 (100 % EtOAc), **m.p.** 185 - 190 °C; **IR** ν_{max}/cm^{-1} 3242, 3079, 2953, 1614, 1583, 1482, 1257; **^{1}H NMR** (400MHz, $CDCl_3$); 7.61 (1H, s, H-5''), 7.40 (2H, appt, J = 7.5 Hz, ArH), 7.34 (1H, appq, J = 8.0 Hz, ArH), 7.09 (1H, s, H-7), 7.01 (1H, t, J = 8.5 Hz, ArH), 6.94 (1H, d, J = 9.5 Hz, H-5), 6.52 (1H, d, J = 9.0 Hz, H-4), 4.82 (2H, t, J = 6.0 Hz, H-1'), 4.47 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 43.5 (C-2'), 47.0 (C-1'), 108.9 (C-4), 112.6 (ArC), 112.8 (ArCH), 115.0 (ArCH), 115.2 (ArC), 115.3 (C-7), 119.9 (C-5), 121.1 (C-5''), 121.3 (ArCH), 123.2 (ArC), 130.4 (ArCH), 132.2 (ArC), 138.5 (ArC), 143.9 (Ar(OCF_3)), 147.1 (ArC), 160.8 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{14}F_4N_5OS$ requires 424.09, found 424.08.

^{1}H NMR

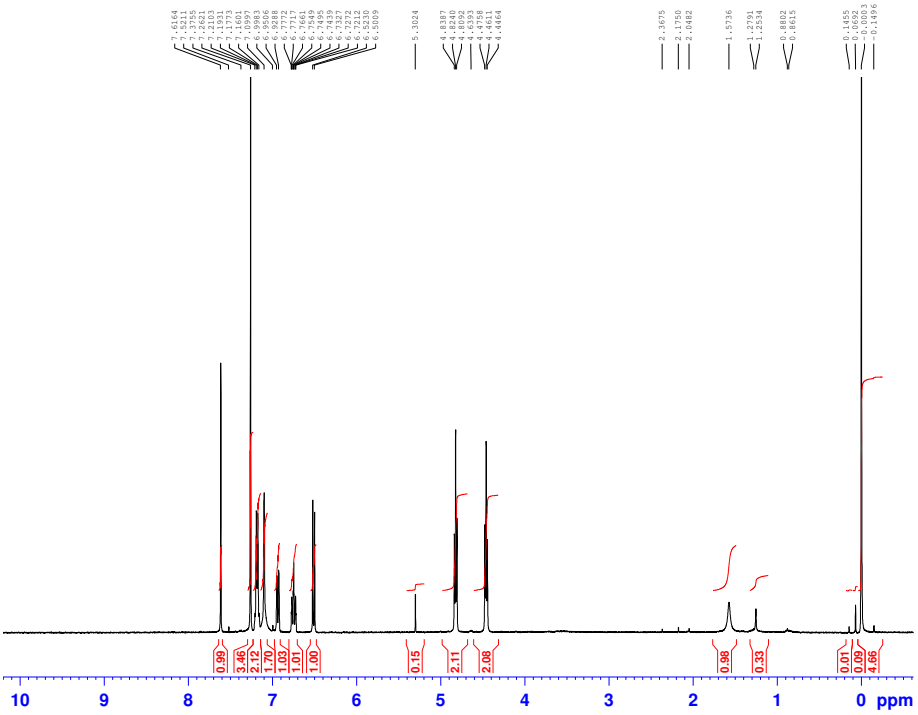


3-(2-(4-(2,4-Difluorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5ab

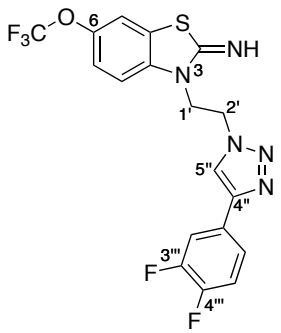


Using the general procedure; to a solution of azide **6** (0.31 g, 1.02 mmol, 1.0 equiv.) and 1-ethynyl-2,4-difluorobenzene (0.2 mL, 1.53 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 1.0 mL 1M $CuSO_4$ (aq) and 2.0 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. The crude was column purified using 100 % EtOAc to yield 3-(2-(4-(2,4-difluorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5ab**, 0.22 g, 0.51 mmol, 50 %) as an off-white solid; **R_f** 0.33 (100 % EtOAc), **m.p.** 194 - 200 °C; **IR** ν_{max}/cm^{-1} 3234, 3028, 1578, 1483, 1257; **^{1}H NMR** (400MHz, $CDCl_3$); 8.16 (1H, td, J = 5.0 Hz and 9.0 Hz, ArH), 7.71 (1H, d, J = 3.5 Hz, H-5''), 7.09 (1H, s, H-7), 6.97 (1H, td, J = 3.0 Hz and 9.0 Hz, ArH), 6.91 (1H, d, J = 7.0 Hz, H-5), 6.83 (1H, ddd, J = 2.5 Hz, 9.0 Hz and 11.0 Hz, ArH), 6.49 (1H, d, J = 9.0 Hz, H-4), 4.83 (2H, t, J = 6.0 Hz, H-1'), 4.47 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 43.5 (C-2'), 46.9 (C-1'), 103.8 (ArC), 104.0 (ArCH), 104.3 (ArC), 108.8 (C-4), 111.9 (ArCH), 112.1 (ArC), 114.6 (ArC), 115.3 (C-7), 119.1 (ArC), 119.8 (C-5), 123.3 (C-5''), 123.4 (ArC), 128.8 (ArCH), 138.5 (ArC), 140.8 (ArC), 143.8 (Ar(OCF_3)); **MS** m/z $[M+H]^+$ $C_{18}H_{13}F_5N_5OS$ requires 442.08, found 442.08.

^{1}H NMR

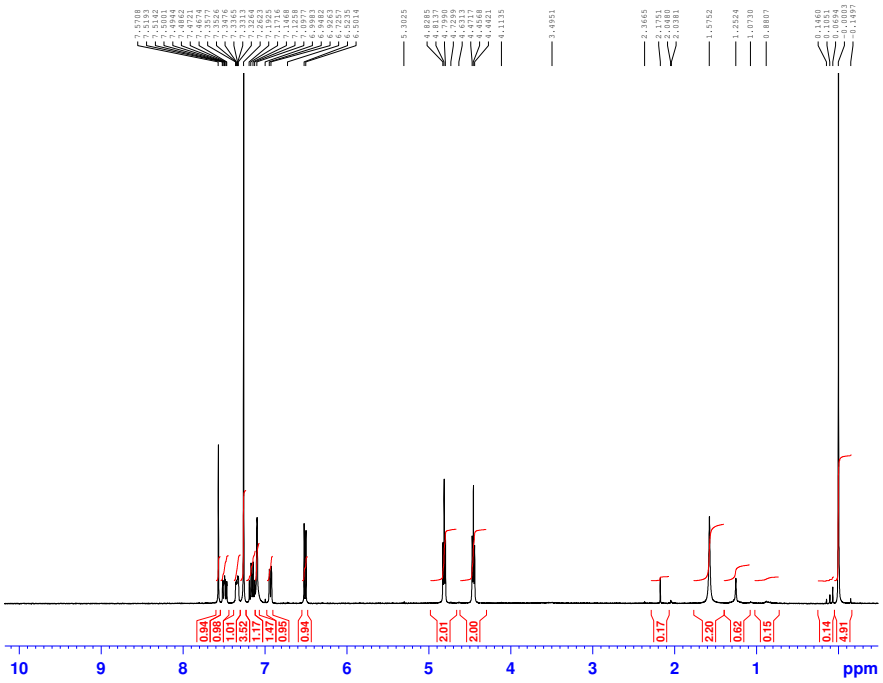


3-(2-(4-(3,4-Difluorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5ac

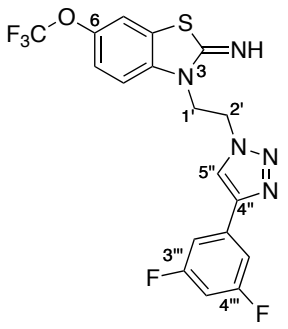


Using the general procedure; to a solution of azide **6** (0.15 g, 0.51 mmol, 1.0 equiv.) and 3,4-difluorophenylacetylene (0.1 mL, 0.76 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 1.0 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(3,4-difluorophenyl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5ac**, 0.10 g, 0.23 mmol, 44 %) as an off-white solid; **R_f** 0.17 (100 % EtOAc), **m.p.** 179 - 184 °C; **IR** ν_{max}/cm^{-1} 3227, 3043, 1580, 1483, 1266; **^{1}H NMR** (400MHz, $CDCl_3$); 7.57 (1H, s, H-5''), 7.50 (1H, dddd, J = 2.0 Hz, 7.5 Hz and 10.0 Hz, ArH), 7.36 - 7.33 (1H, m, ArH), 7.16 (1H, q, J = 8.5 Hz, ArH), 7.10 (1H, s, H-7), 6.94 (1H, d, J = 8.5 Hz, H-5), 6.51 (1H, d, J = 9.0 Hz, H-4), 4.82 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.4 (C-2'), 45.9 (C-1'), 107.8 (C-4), 113.9 (ArC), 114.3 (ArCH), 116.6 (C-7), 116.7 (ArCH), 118.8 (C-5), 119.9 (C-5''), 120.7 (ArC), 122.2 (ArCH), 126.2 (ArC), 137.5 (ArC), 142.8 (Ar(OCF_3)), 145.3 (ArC), 148.2 (ArC), 150.6 (ArC), 159.7 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{13}F_5N_5OS$ requires 442.08, found 442.07.

^{1}H NMR

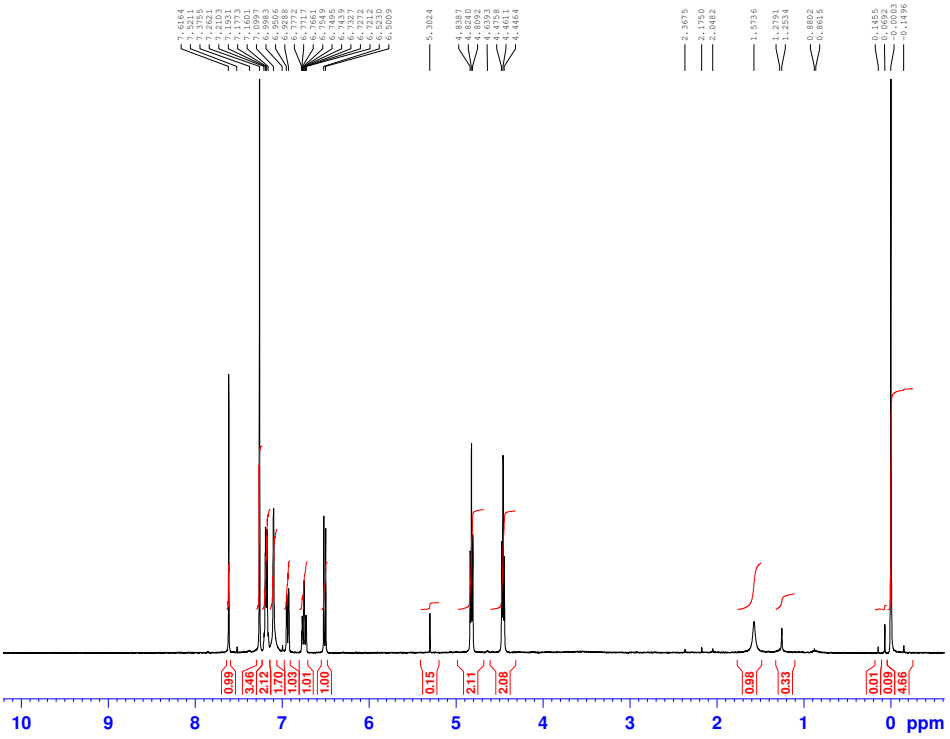


3-(2-(4-(2,4-Difluorophenyl)-1,2,3-triazol-1-ly)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5ad

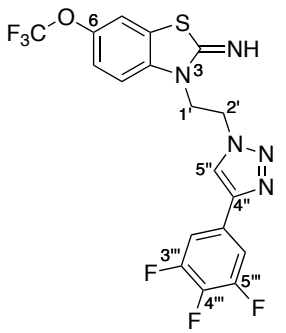


Using the general procedure; to a solution of azide **6** (0.19 g, 0.61 mmol, 1.0 equiv.) and 1-ethynyl-3,5-difluorobenzene (0.1 mL, 0.92 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.6 mL $CuSO_4$ (aq) and 1.2 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(2,4-difluorophenyl)-1,2,3-triazol-1-ly)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5ad**, 0.11 g, 0.25 mmol, 41 %) as an off-white solid; $\mathbf{R_f}$ 0.23 (100 % EtOAc), **m.p.** 183 - 185 °C; **IR** ν_{max}/cm^{-1} 3259, 3087, 1617, 1588, 1484, 1262; **^{1}H NMR** (400MHz, $CDCl_3$); 7.62 (1H, s, H-5''), 7.19 (2H, d, J = 6.5 Hz, ArH), 7.10 (1H, s, H-7), 6.94 (1H, d, J = 8.5 Hz, H-5), 6.75 (1H, tt, J = 2.0 Hz and 9.0 Hz, ArH), 6.51 (1H, d, J = 9.0 Hz, H-4), 4.83 (2H, t, J = 6.0 Hz, H-1'), 4.47 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.4 (C-2'), 46.0 (C-1'), 102.5 (ArCH), 107.4 (ArCH), 107.6 (ArC), 107.8 (C-4), 114.3 (C-7), 118.8 (C-5), 120.4 (C-5''), 122.2 (ArC), 132.1 (ArC), 137.4 (ArC), 142.8 (Ar(OCF_3)), 145.1 (ArC), 161.1 (ArC), 163.5 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{13}F_5N_5OS$ requires 442.08, found 442.07.

^{1}H NMR

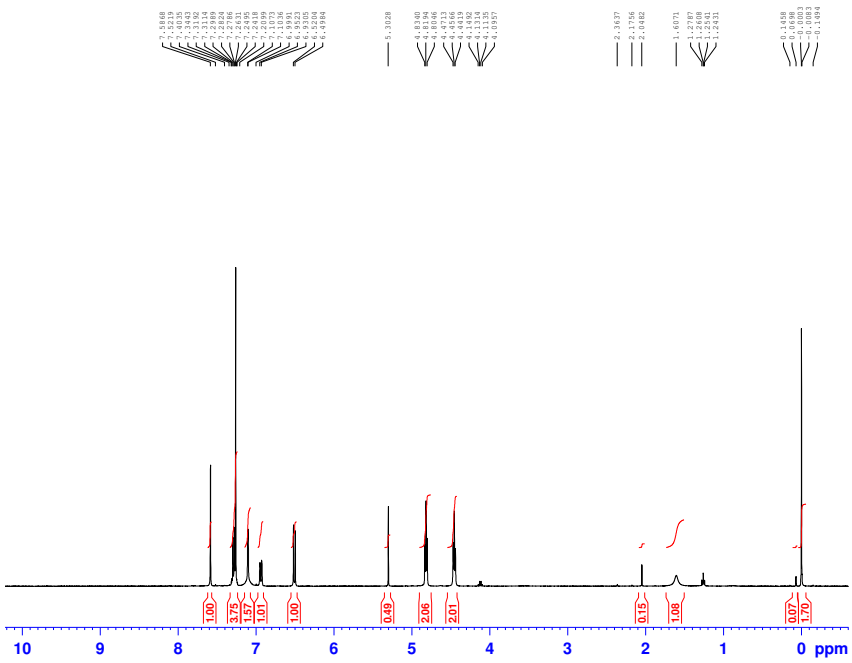


6-(Trifluoromethoxy)-3-(2-(4-(3,4,5-trifluorophenyl)-1,2,3-triazol-1yl)ethyl)benzothiazol-2-imine 5ae



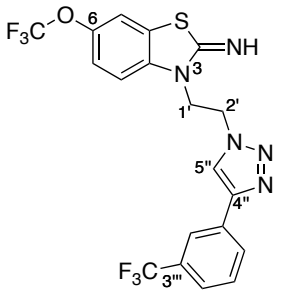
Using the general procedure; to a solution of azide **6** (0.14 g, 0.46 mmol, 1.0 equiv.) and 3,4,5-trifluorophenylacetylene (0.11 g, 0.69 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 0.9 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 6-(trifluoromethoxy)-3-(2-(4-(3,4,5-trifluorophenyl)-1,2,3-triazol-1yl)ethyl)benzothiazol-2-imine (**5ae**, 0.16 g, 0.34 mmol, 74 %) as a pale yellow solid; **R_f** 0.21 (100 % EtOAc), **m.p.** 166 - 170 °C; **IR** ν_{max}/cm^{-1} 3229, 3077, 1607, 1518, 1483, 1257; **^{1}H NMR** (400MHz, $CDCl_3$); 7.59 (1H, s, H-5''), 7.32 - 7.24 (2H, m, ArH), 7.11 (1H, d, J = 1.5 Hz, H-7), 6.94 (1H, d, J = 8.5 Hz, H-5), 6.51 (1H, d, J = 9.0 Hz, H-4), 4.82 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 43.4 (C-2'), 47.0 (C-1'), 108.8 (C-4), 109.7 (ArCH), 109.9 (ArCH), 115.4 (C-7), 119.9 (C-5), 121.2 (C-5''), 123.2 (ArC), 138.6 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{12}F_6N_5OS$ requires 460.07, found 460.07.

^{1}H NMR



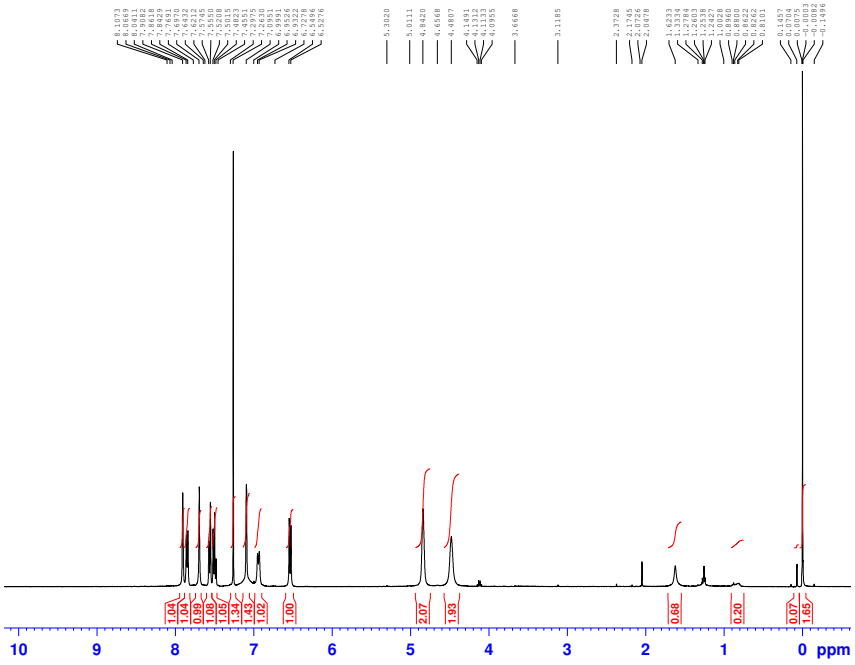
6-(Trifluoromethoxy)-3-(2-(4-(3-(trifluoromethyl)phenyl)-1,2,3-triazol-1-yl)ethyl)benzothiazol-2-imine

5af

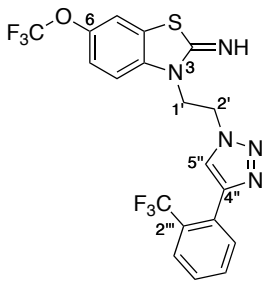


Using the general procedure; to a solution of azide **6** (0.18 g, 0.59 mmol, 1.0 equiv.) and 3-ethynyl-α,α,α-trifluorotoluene (0.1 mL, 0.88 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.6 mL 1M $CuSO_4$ (aq) and 1.2 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 6-(trifluoromethoxy)-3-(2-(4-(3-(trifluoromethyl)phenyl)-1,2,3-triazol-1-yl)ethyl)benzothiazol-2-imine (**5af**, 0.18 g, 0.39 mmol, 66 %) as a yellow/green solid; **R_f** 0.21 (100 % EtOAc), **m.p.** 145 - 149 °C; **IR** ν_{max}/cm^{-1} 3246, 3071, 1578, 1483, 1322, 1253; **^{1}H NMR** (400MHz, $CDCl_3$); 7.91 (1H, s, ArH), 7.85 (1H, d, J = 7.5 Hz, ArH), 7.70 (1H, s, H-5''), 7.57 (1H, d, J = 8.0 Hz, ArH), 7.50 (1H, t, J = 7.5 Hz, ArH), 7.10 (1H, s, H-7), 6.94 (1H, d, J = 8.0 Hz, H-5), 6.54 (1H, d, J = 9.0 Hz, H-4), 4.84 (2H, bs, H-1'), 4.48 (2H, bs, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.4 (C-2'), 45.9 (C-1'), 107.8 (C-4), 114.3 (C-7), 118.8 (C-5), 120.3 (C-5''), 120.6 (ArC), 121.4 (ArCH), 121.6 (ArC), 122.2 (Ar(CF_3), 123.8 (ArCH), 124.3 (ArC), 127.8 (ArCH), 128.3 (ArCH), 130.1 (ArC), 130.4 (ArC), 137.5 (Ar(OCF_3)), 142.8 (ArC), 145.8 (ArC); **MS** m/z $[M+H]^+$ $C_{19}H_{14}F_6N_5OS$ requires 474.08, found 474.08.

^{1}H NMR

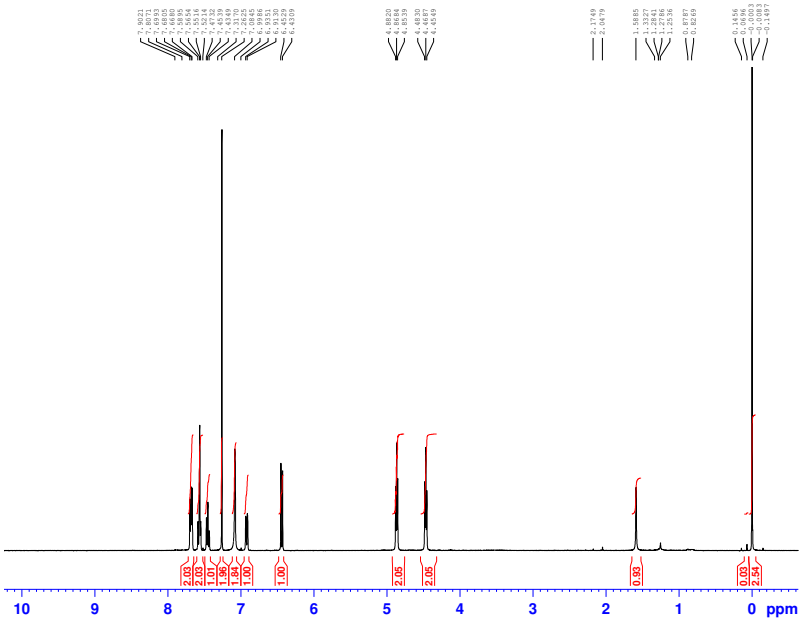


6-(Trifluoromethoxy)-3-(2-(4-(2-(trifluoromethyl)phenyl)-1,2,3-triazol-1-yl)ethyl)benzothiazol-2-imine 5ag



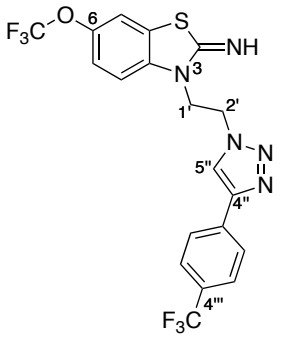
Using the general procedure; to a solution of azide **6** (0.22 g, 0.74 mmol, 1.0 equiv.) and 2-ethynyl-α,α,α-trifluorotoluene (0.2 mL, 1.11 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.5 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 6-(trifluoromethoxy)-3-(2-(4-(2-(trifluoromethyl)phenyl)-1,2,3-triazol-1-yl)ethyl)benzothiazol-2-imine (**5ag**, 0.21 g, 0.43 mmol, 59 %) as an off white solid; **R_f** 0.32 (100 % EtOAc), **m.p.** 186 - 190 °C; **IR** ν_{max}/cm^{-1} 3245, 3081, 1616, 1585, 1485, 1318, 1256; **^{1}H NMR** (400MHz, $CDCl_3$); 7.69 (2H, t, J = 7.5 Hz, ArH), 7.57 (2H, t, J = 9.5 Hz, ArH and H-5''), 7.45 (1H, t, J = 7.5 Hz, ArH), 7.08 (1H, s, H-7), 6.93 (1H, d, J = 9.0 Hz, H-5), 6.45 (1H, d, J = 9.0 Hz, H-4), 4.87 (2H, t, J = 5.5 Hz, H-1'), 4.47 (2H, t, J = 5.5 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.8 (C-2'), 46.0 (C-1'), 107.7 (C-4), 114.2 (C-7), 118.7 (C-4), 122.2 (ArC), 123.0 (Ar(CF_3)), 124.2 (C-5''), 125.0 (ArC), 126.2 (ArCH), 126.5 (ArC), 127.3 (ArC), 128.0 (ArCH), 130.6 (ArCH), 130.9 (ArCH), 137.6 (Ar(OCF_3)), 142.7 (ArC), 143.6 (ArC), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{19}H_{14}F_6N_5OS$ requires 474.08, found 474.08.

^{1}H NMR



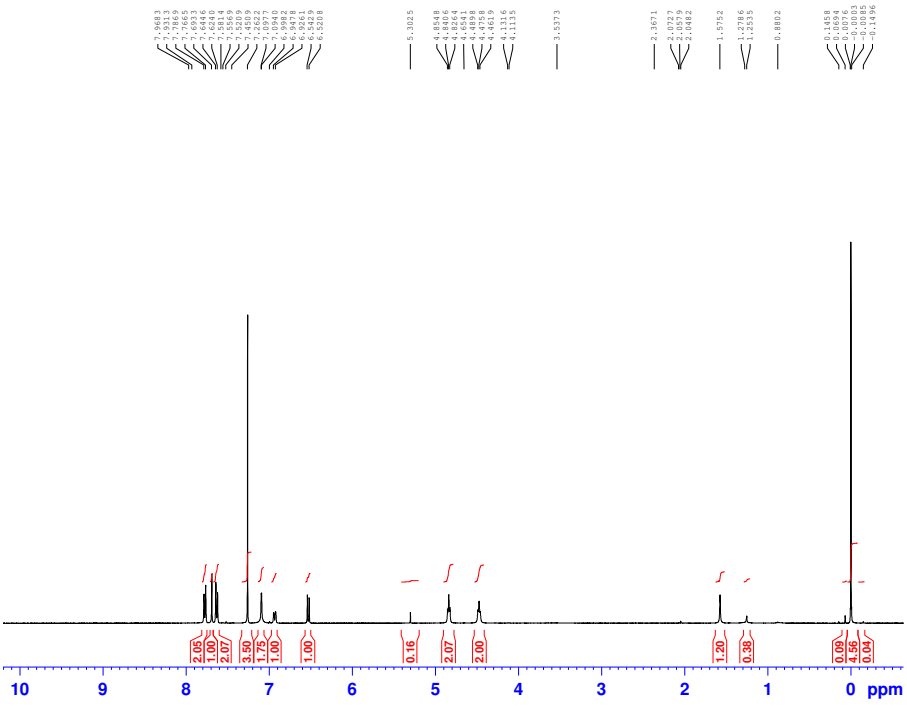
6-(Trifluoromethoxy)-3-(2-(4-(4-(trifluoromethyl)phenyl)-1,2,3-triazol-1-yl)ethyl)benzothiazol-2-imine

5ah

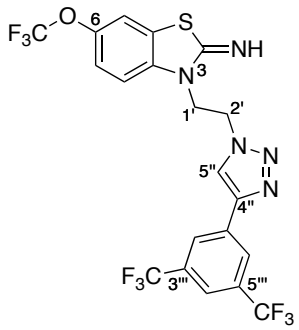


Using the general procedure; to a solution of azide **6** (0.22 g, 0.72 mmol, 1.0 equiv.) and 4-ethynyl-α,α,α-trifluorotoluene (0.2 mL, 1.09 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.4 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 6-(trifluoromethoxy)-3-(2-(4-(4-(trifluoromethyl)phenyl)-1,2,3-triazol-1-yl)ethyl)benzothiazol-2-imine (**5ah**, 0.12 g, 0.25 mmol, 35 %) as a pale yellow solid; **R_f** 0.17 (100 % EtOAc), **m.p.** 218 - 221 °C; **IR** ν_{max}/cm^{-1} 3253, 3021, 1613, 1584, 1484, 1326, 1234; **^{1}H NMR** (400MHz, $CDCl_3$); 7.78 (2H, d, J = 8.0 Hz, ArH), 7.69 (1H, s, H-5''), 7.63 (2H, d, J = 8.0 Hz, ArH), 7.10 (1H, d, J = 1.5 Hz, H-7), 6.94 (1H, d, J = 8.5 Hz, H-5), 6.53 (1H, d, J = 9.0 Hz, H-4), 4.84 (2H, t, J = 5.5 Hz, H-1'), 4.48 (2H, t, J = 5.5 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 43.5 (C-2'), 47.0 (C-1'), 108.9 (C-4), 115.5 (C-7), 119.9 (C-5), 121.6 (C-5''), 122.7 (ArC), 123.3 (Ar(CF_3)), 123.7 (ArC), 125.8 (ArCH), 129.7 (ArC), 130.0 (ArC), 130.3 (ArC), 133.6 (ArC), 138.6 (Ar(OCF_3)), 143.9 (ArC), 146.8 (ArC); **MS** m/z $[M+H]^+$ $C_{19}H_{14}F_6N_5OS$ requires 474.08, found 474.08.

^{1}H NMR

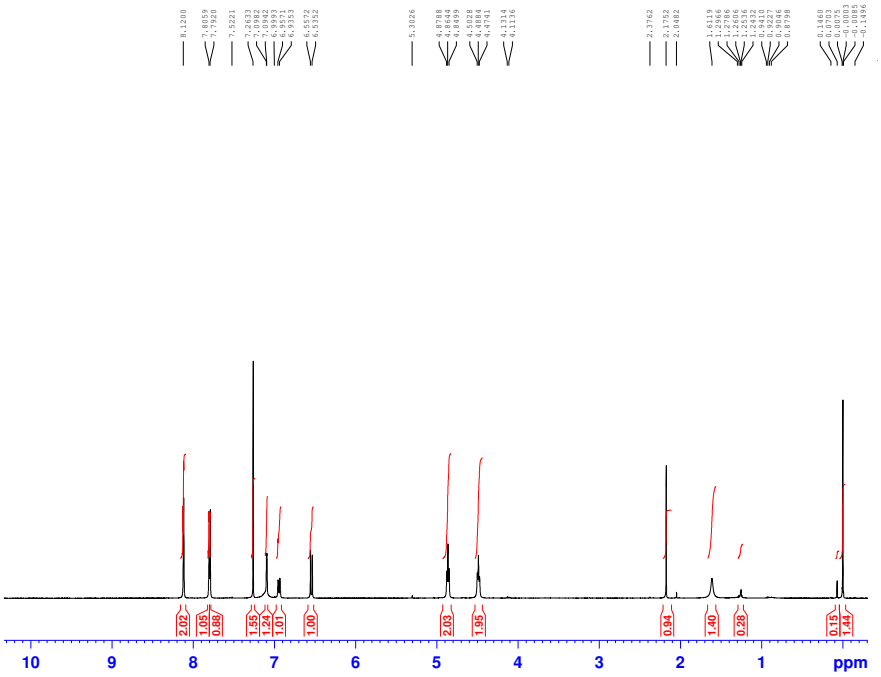


6-(Trifluoromethyoxy)-3-(2-(4-(3,5-bis(trifluoromethyl)phenyl)-1,2,3-triazol-1-ly)ethyl)benzothiazol-2-imine 5ai

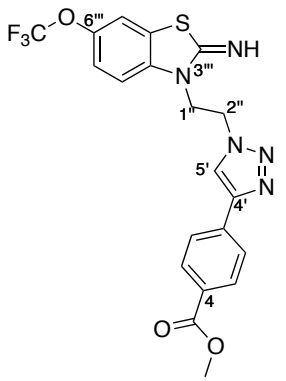


Using the general procedure; to a solution of azide **6** (0.14 g, 0.47 mmol, 1.0 equiv.) and 1-ethynyl-3,5-bis(trifluoromethyl) benzene (0.1 mL, 0.71 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 0.9 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 6-(trifluoromethyoxy)-3-(2-(4-(3,5-bis(trifluoromethyl)phenyl)-1,2,3-triazol-1-ly)ethyl)benzothiazol-2-imine (**5ai**, 0.22 g, 0.41 mmol, 87 %) as a pale yellow solid; **R_f** 0.31 (100 % EtOAc), **m.p.** 184 - 188 °C; **IR** ν_{max}/cm^{-1} 3217, 3043, 1624, 1587, 1484, 1324, 1275; **^{1}H NMR** (400MHz, $CDCl_3$); 8.12 (2H, s, ArH), 7.81 (1H, s, ArH), 7.79 (1H, s, H-5''), 7.10 (1H, d, J = 1.5 Hz, H-7), 6.95 (1H, d, J = 8.5 Hz, H-5), 6.55 (1H, d, J = 9.0 Hz, H-4), 4.87 (2H, t, J = 6.0 Hz, H-1'), 4.49 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 43.3 (C-2'), 47.1 (C-1'), 108.8 (C-4), 115.4 (C-7), 119.9 (C-5), 121.8 (C-5''), 121.9 (ArCH), 123.3 (ArC), 124.5 (ArC), 125.6 (ArCH), 132.1 (ArC), 132.2 (ArC), 132.5 (ArC), 143.9 (ArC), 145.4 (ArC); **MS** m/z $[M+H]^+$ $C_{20}H_{13}F_9N_5OS$ requires 542.07, found 542.07.

^{1}H NMR

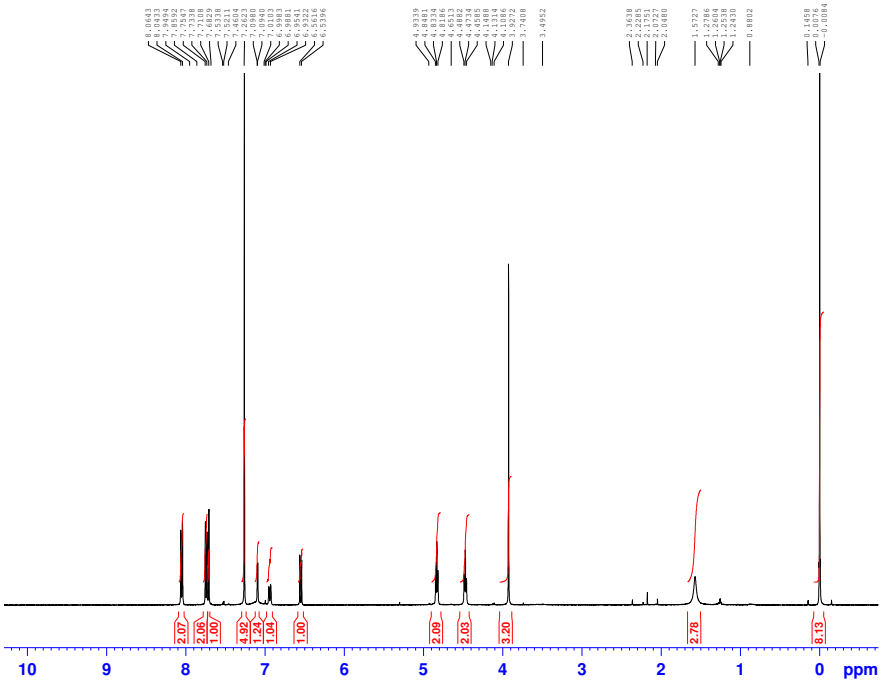


Methyl 4-(1-(2-(2-imino-6-(trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl)benzoate 5aj

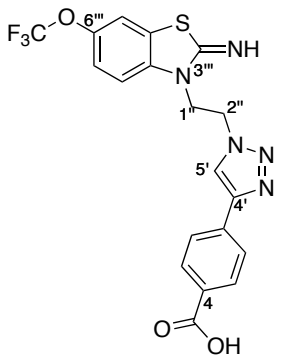


Using the general procedure; to a solution of azide **6** (0.14 g, 0.45 mmol, 1.0 equiv.) and methyl-4-ethynylbenzoate (0.11 g, 0.67 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 0.9 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield methyl 4-(1-(2-(2-imino-6-(trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl)benzoate (**5aj**, 0.12 g, 0.26 mmol, 59 %) as an off white solid; **R_f** 0.19 (100 % EtOAc), **m.p.** 196 - 199 °C; **IR** ν_{max}/cm^{-1} 3276, 3099, 1721, 1604, 1582, 1485, 1261; **^{1}H NMR** (400MHz, $CDCl_3$); 8.05 (2H, d, J = 8.5 Hz, ArH), 7.74 (2H, d, J = 8.5 Hz, ArH), 7.71 (1H, s, H-5'), 7.10 (1H, d, J = 1.5 Hz, H-7'''), 6.94 (1H, d, J = 8.5 Hz, H-5'''), 6.55 (1H, d, J = 9.0 Hz, H-4'''), 4.84 (2H, t, J = 6.0 Hz, H-1''), 4.48 (2H, t, J = 6.0 Hz, H-2''), 3.93 (3H, s, $O(CH_3)$); **^{13}C NMR** (100MHz, $CDCl_3$); 43.6 (C-2''), 47.0 (C-1''), 52.2 ($O(CH_3)$), 108.9 (C-4'''), 115.3 (C-7'''), 119.8 (C-5'''), 121.6 (C-5'), 125.5 (ArCH), 129.7 (ArC), 130.2 (ArCH); **MS** m/z $[M+H]^+$ $C_{20}H_{17}F_3N_5O_3S$ requires 464.10, found 464.10.

^{1}H NMR

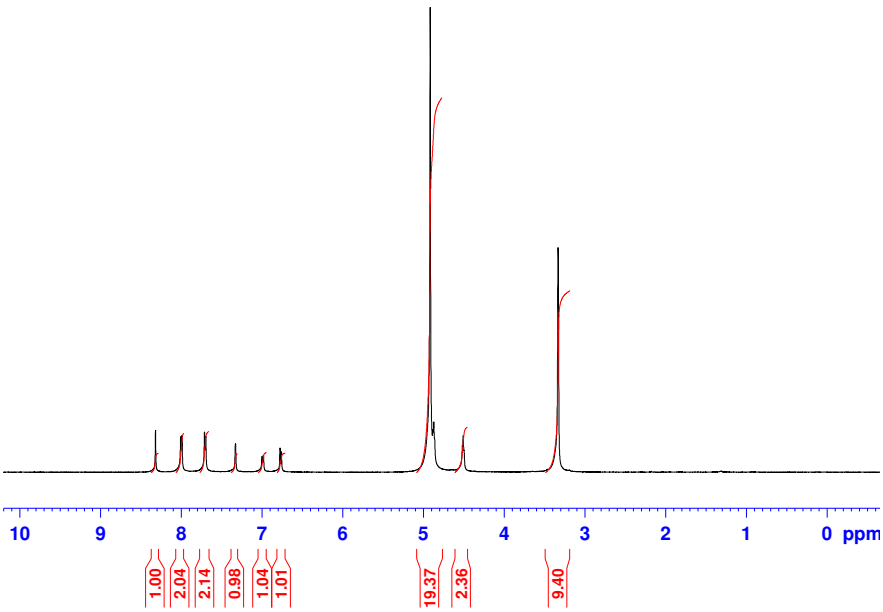


4-(1-(2-(2-Imino-6-(trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl)benzoic acid 5ak

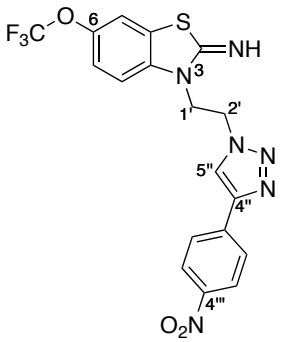


Using the general procedure; to a solution of azide **6** (0.16 g, 0.53 mmol, 1.0 equiv.) and 4-ethynylbenzoic acid (0.12 g, 0.79 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 1.0 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. Once washed with brine a precipitate formed. This was filtered to yield 4-(1-(2-(2-imino-6-(trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl)benzoic acid (**5ak**, 0.14 g, 0.31 mmol, 59 %) as an off-white solid; **m.p.** 380 - 384 °C; **IR** ν_{max}/cm^{-1} 3238, 1585, 1484, 1262; **^{1}H NMR** (500MHz, MeOD); 8.32 (1H, s, H-5'), 8.00 (2H, d, J = 10.0 Hz, ArH), 7.71 (2H, d, J = 5.0 Hz, ArH), 7.33 (1H, s, H-7'''), 6.99 (1H, d, J = 10.0 Hz, H-5'''), 6.77 (1H, d, J = 10.0 Hz, H-4'''), 4.88 (2H, t, J = 5.0 Hz, H-1''), 4.52 (2H, t, J = 5.0 Hz, H-2''); **^{13}C NMR** (125MHz, MeOD); 42.6 (C-2''), 46.7 (C-1''), 109.3 (C-4'''), 115.2 (C-7'''), 119.0 (C-5'''), 122.4 (C-5'), 124.7 (ArCH), 129.5 (ArCH), 132.1 (ArC), 138.8 (ArC), 143.9 (ArC), 147.5 (ArC); **MS** m/z $[M+H]^+$ $C_{19}H_{15}F_3N_5O_3S$ requires 450.09, found 450.08.

^{1}H NMR

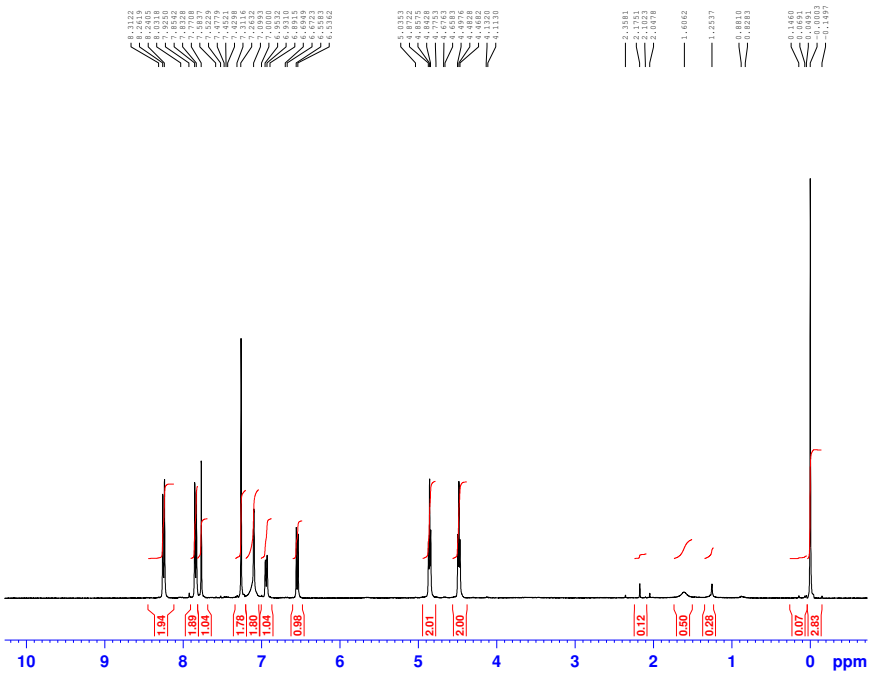


3-(2-(4-(4-Nitrophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine 5al

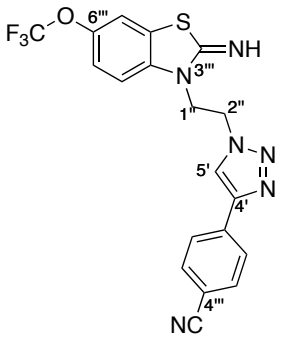


Using the general procedure; to a solution of azide **6** (0.15 g, 0.48 mmol, 1.0 equiv.) and 1-ethynyl-4-nitrobenzene (0.11 g, 0.72 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 1.0 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(4-nitrophenyl)-1,2,3-triazol-1-yl)ethyl)-6-trifluoromethoxy)benzothiazol-2-imine (**5al**, 0.14 g, 0.30 mmol, 63 %) as a pale yellow solid; **R_f** 0.15 (100 % EtOAc), **m.p.** 181 - 186 °C; **IR** ν_{max}/cm^{-1} 3322, 3077, 1605, 1581, 1514, 1484, 1331, 1257; **^{1}H NMR** (400MHz, $CDCl_3$); 8.25 (2H, d, J = 8.5 Hz, ArH), 7.84 (2H, d, J = 8.5 Hz, ArH), 7.77 (1H, s, H-5''), 7.10 (1H, s, H-7), 6.94 (1H, d, J = 9.0 Hz, H-5), 6.55 (1H, d, J = 9.0 Hz, H-4), 4.86 (2H, t, J = 6.0 Hz, H-1'), 4.49 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.3 (C-2'), 46.0 (C-1'), 107.8 (C-4), 114.5 (C-7), 118.8 (C-5), 120.6 (ArC), 121.3 (C-5''), 122.3 (ArC), 123.2 (ArCH), 125.1 (ArC), 135.4 (ArC), 137.4 (ArC), 142.8 (Ar(OCF_3)), 144.8 (ArC), 146.3 (ArC), 159.7 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{14}F_3N_6O_3S$ requires 451.08, found 451.08.

^{1}H NMR

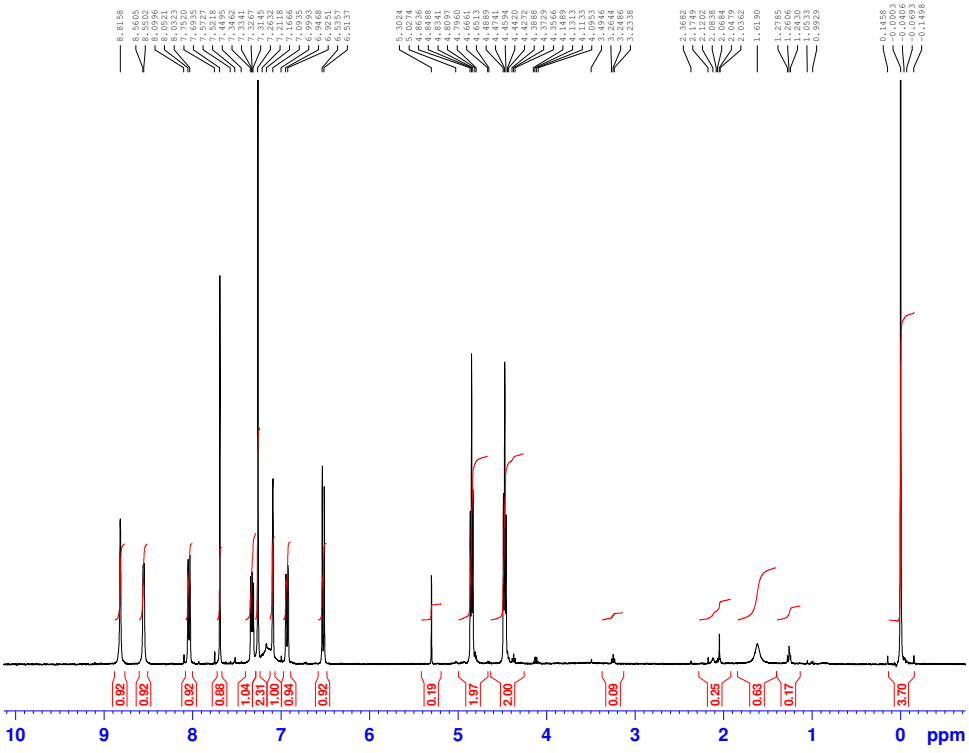


4-(1-(2-(2-Imino-6-(trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl) benzonitrile 5am

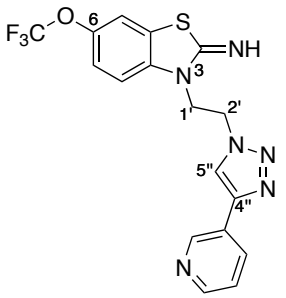


Using the general procedure; to a solution of azide **6** (0.21 g, 0.70 mmol, 1.0 equiv.) and 4-ethynylbenzonitrile (0.13 g, 1.05 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.4 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 4-(1-(2-(2-imino-6-(trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazol-4-yl) benzonitrile4 (**5am**, 0.18 g, 0.32 mmol, 59 %) as an off-white solid; **R_f** 0.12 (100 % EtOAc), **m.p.** 193 - 198 °C; **IR** ν_{max}/cm^{-1} 3320, 3048, 2222, 1612, 1584, 1483, 1252; **^{1}H NMR** (400MHz, $CDCl_3$); 7.77 (2H, d, J = 8.0 Hz, ArH), 7.71 (1H, s, H-5'), 7.67 (2H, d, J = 8.0 Hz, ArH), 7.10 (1H, s, H-7'''), 6.93 (1H, d, J = 8.5 Hz, H-5'''), 6.53 (1H, d, J = 9.0 Hz, H-4'''), 4.85 (2H, t, J = 6.0 Hz, H-1''), 4.48 (2H, t, J = 6.0 Hz, H-2''); **^{13}C NMR** (100MHz, $CDCl_3$) 43.4 (C-2''), 47.0 (C-1''), 108.8 (C-4'''), 111.7 (ArC), 115.4 (C-7'''), 118.7 (Ar(CN)), 119.1 (ArC), 119.9 (C-5'''), 121.9 (C-5'), 123.3 (ArC), 126.1 (ArCH), 132.7 (ArCH), 134.5 (ArC), 138.5 (ArC), 143.8 (Ar(OCF_3)), 146.3 (ArC), 160.8 (ArC); **MS** m/z $[M+H]^+$ $C_{19}H_{14}F_3N_6OS$ requires 431.09, found 431.09.

^{1}H NMR

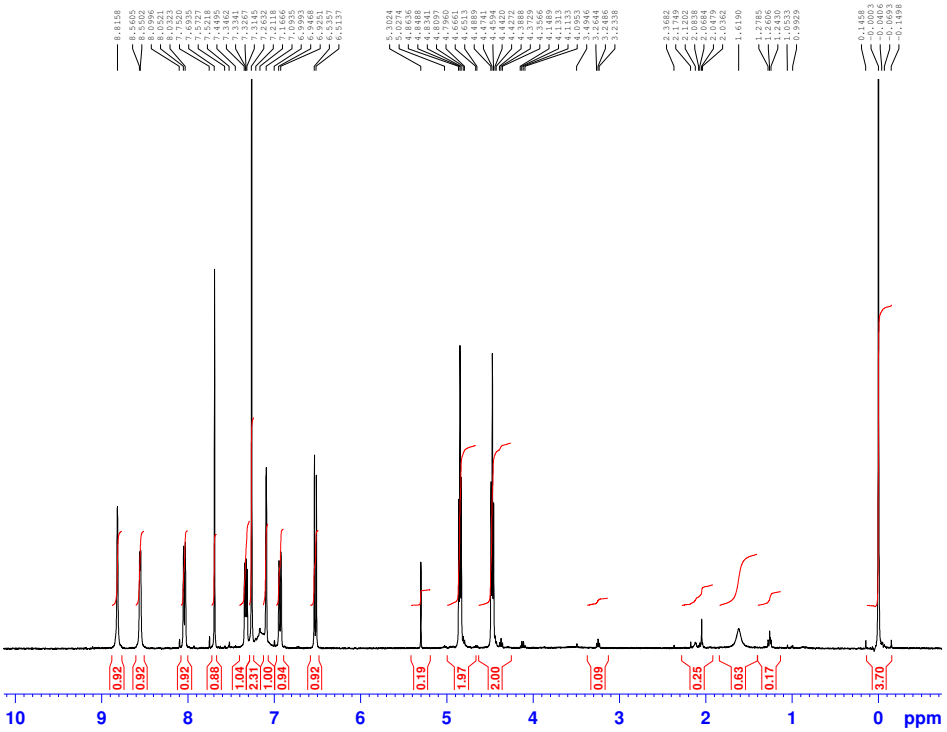


3-(2-(4-(Pyridin-3-yl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5an

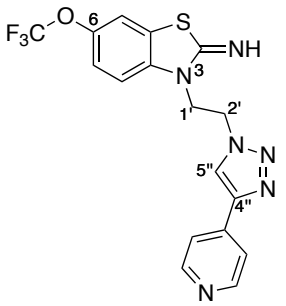


Using the general procedure; to a solution of azide **6** (0.16 g, 0.51 mmol, 1.0 equiv.) and 3-ethynylpyridine (0.08 g, 0.77 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 1.0 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2.5 h. After work-up the crude was column purified using a gradient solvent system from 100 % EtOAc to 100 % MeOH to yield 3-(2-(4-(pyridin-3-yl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5an**, 0.13 g, 0.32 mmol, 64 %) as a pale yellow solid; $\mathbf{R_f}$ 0.08 (100 % EtOAc), **m.p.** 195 - 197 °C; **IR** ν_{max}/cm^{-1} 3217, 3035, 1618, 1585, 1482, 1262; **^{1}H NMR** (400MHz, $CDCl_3$); 8.82 (1H, s, CH(Py.)), 8.56 (1H, d, J = 4.0 Hz, CH(Py.)), 8.04 (1H, d, J = 8.0 Hz, CH(Py.)), 7.69 (1H, s, H-5''), 7.33 (1H, q, J = 5.0 Hz, CH(Py.)), 7.09 (1H, s, H-7), 6.94 (1H, d, J = 8.5 Hz, H-5), 6.53 (1H, d, J = 9.0 Hz, H-4), 4.84 (2H, t, J = 6.0 Hz, H-1'), 4.48 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.4 (C-2'), 45.9 (C-1'), 107.8 (C-4), 114.3 (C-7), 118.8 (C-5), 120.1 (C-5''), 120.6 (ArC), 122.2 (ArC), 122.7 (ArC), 125.3 (CH(Py.)), 132.0 (CH(Py.)), 137.4 (ArC), 142.8 (Ar(OCF_3)), 144.0 (ArC), 145.9 (CH(Py.)), 148.3 (CH(Py.)), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{17}H_{14}F_3N_6OS$ requires 407.09, found 407.09.

^{1}H NMR

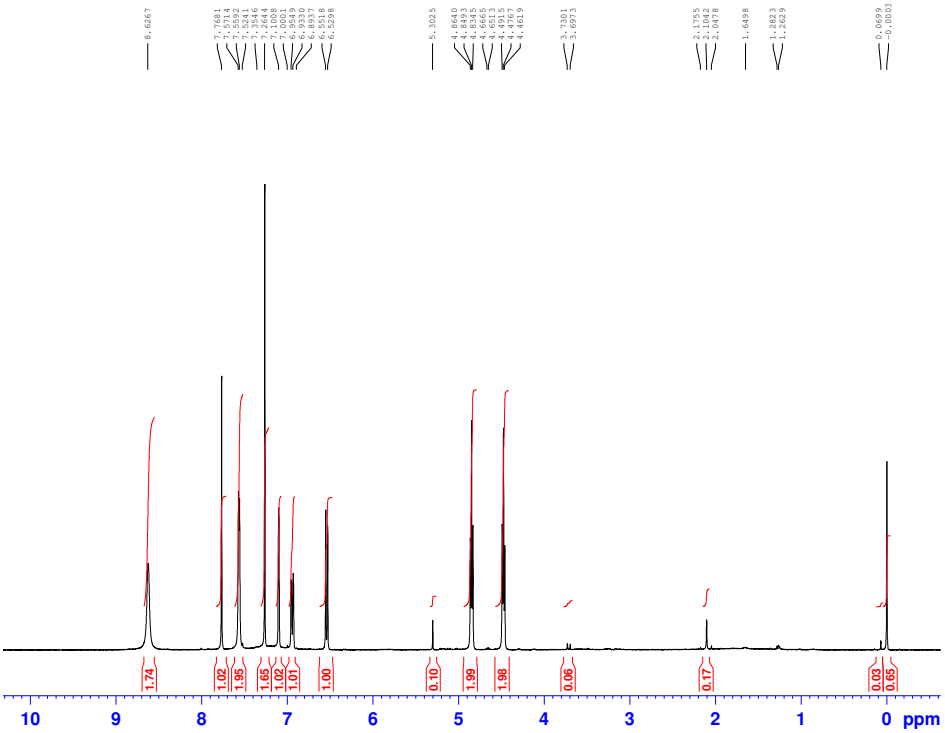


3-(2-(4-(Pyridin-4-yl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5ao

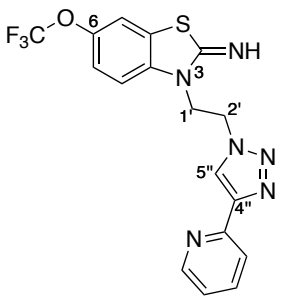


Using the general procedure; to a solution of azide **6** (0.25 g, 0.82 mmol, 1.0 equiv.) and 4-ethynylpyridine (0.17 g, 1.23 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.8 mL 1M $CuSO_4$ (aq) and 1.6 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 9:1 DCM:MeOH to yield 3-(2-(4-(pyridin-4-yl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5ao**, 0.15 g, 0.38 mmol, 46 %) as an off white solid; **R_f** 0.21 (9:1 DCM:MeOH), **m.p.** 209 - 211 °C; **IR** ν_{max}/cm^{-1} 3221, 3028, 1604, 1583, 1482, 1266; **^{1}H NMR** (400MHz, $CDCl_3$); 8.63 (2H, bs, CH(Py.)), 7.77 (1H, s, H-5''), 7.57 (2H, d, J = 5.0 Hz, CH(Py.)), 7.10 (1H, s, H-7), 6.91 (1H, d, J = 9.0 Hz, H-5), 6.54 (1H, d, J = 9.0 Hz, H-4), 4.85 (2H, t, J = 6.0 Hz, H-1'), 4.48 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.4 (C-2'), 46.0 (C-1'), 107.8 (C-4), 114.3 (C-7), 118.0 (ArC), 118.8 (C-5), 120.6 (ArC), 121.2 (CH(Py.)), 122.2 (C-5''), 136.4 (ArC), 137.4 (ArC), 142.8 (Ar(OCF_3)), 144.6 (ArC), 149.4 (CH(Py.)), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{17}H_{14}F_3N_6OS$ requires 407.09, found 407.09.

^{1}H NMR

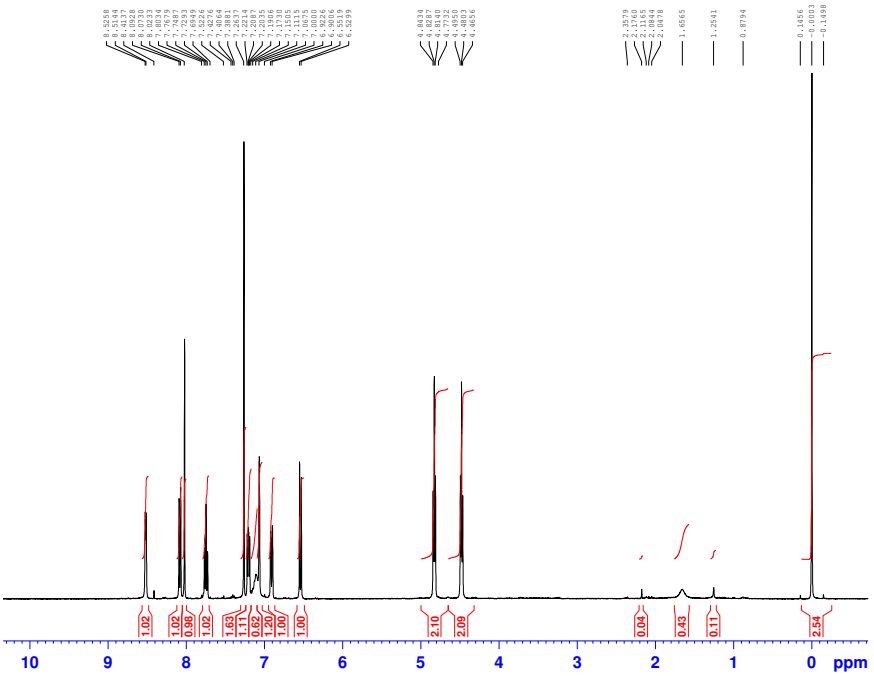


3-(2-(4-(Pyridin-2-yl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5ap

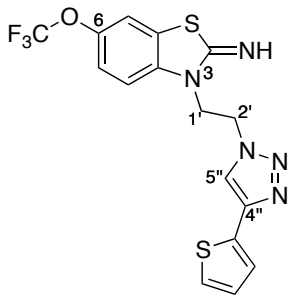


Using the general procedure; to a solution of azide **6** (0.20 g, 0.67 mmol, 1.0 equiv.) and 2-ethynylpyridine (0.1 mL, 1.01 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.3 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using a gradient solvent system from 100 % EtOAc to 100 % MeOH to yield 3-(2-(4-(pyridin-2-yl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5ap**, 0.15 g, 0.36 mmol, 53 %) a pale yellow solid; $\mathbf{R_f}$ 0.07 (100 % EtOAc), **m.p.** 156 - 160 °C; **IR** ν_{max}/cm^{-1} 3206, 3056, 1602, 1581, 1484, 1260; **^{1}H NMR** (400MHz, $CDCl_3$); 8.52 (1H, d, J = 4.5 Hz, CH(Py.)), 8.08 (1H, d, J = 8.0 Hz, CH(Py.)), 8.02 (1H, s, H-5"), 7.75 (1H, t, J = 7.5 Hz, CH(Py.)), 7.21 (1H, t, J = 5.0 Hz, CH(Py.)), 7.11 (1H, bs, NH), 7.07 (1H, s, H-7), 6.91 (1H, d, J = 9.0 Hz, H-5), 6.54 (1H, d, J = 9.0 Hz, H-4), 4.83 (2H, d, J = 6.0 Hz, H-1'), 4.49 (2H, d, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.5 (C-2'), 46.0 (C-1'), 107.8 (C-4), 114.3 (C-7), 119.1 (C-5), 121.9 (CH(Py.)), 122.2 (CH(Py.)), 122.4 (C-5"), 135.8 (CH(Py.)), 137.6 (ArC), 142.7 (Ar(OCF_3)), 144.4 (ArC), 147.6 (ArC), 148.3 (CH(Py.)), 148.8 (ArC), 149.8 (ArC), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{17}H_{14}F_3N_6OS$ requires 407.09, found 407.09.

^{1}H NMR

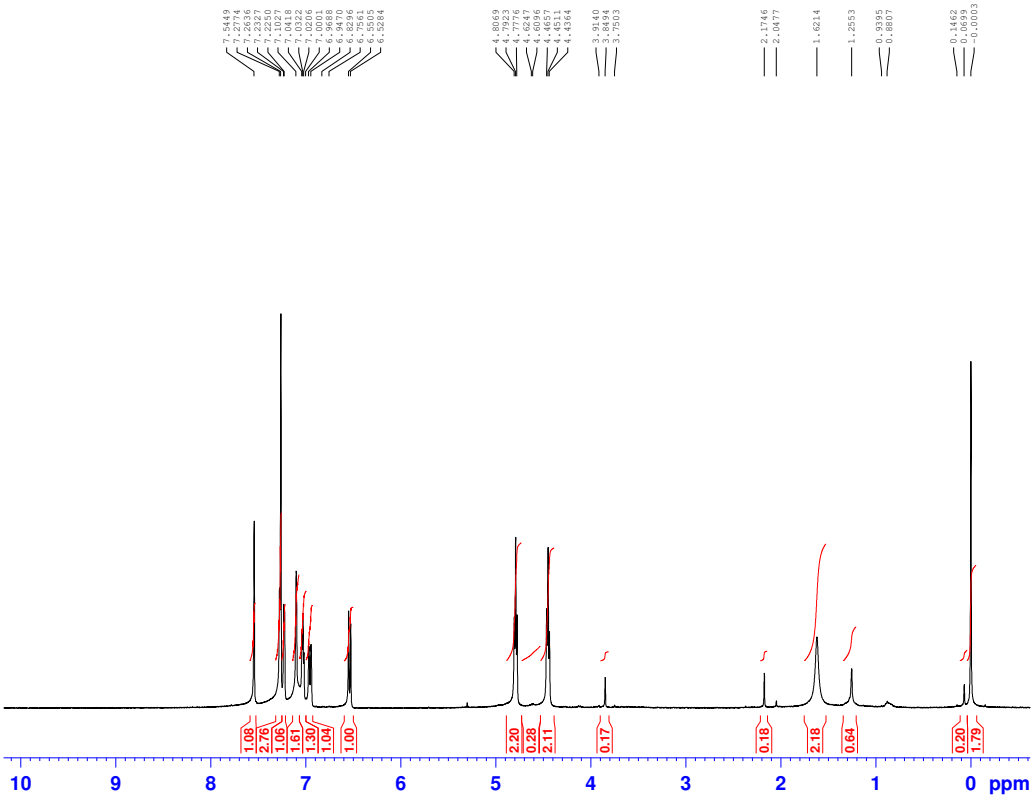


3-(2-(4-(Thiophen-2-yl)-1,2,3-triazol-1-ly)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5aq

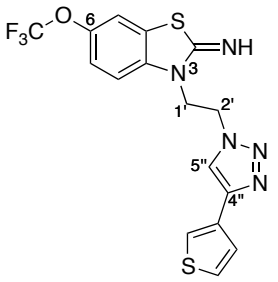


Using the general procedure; to a solution of azide **6** (0.21 g, 0.70 mmol, 1.0 equiv.) and 2-ethynylthiophene (0.1 mL, 1.05 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.4 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(thiophen-2-yl)-1,2,3-triazol-1-ly)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5aq**, 0.15 g, 0.37 mmol, 53 %) as a pale yellow solid; **R_f** 0.19 (100 % EtOAc), **m.p.** 172 - 176 °C; **IR** ν_{max}/cm^{-1} 3245, 3068, 1605, 1583, 1483, 1256; **^{1}H NMR** (400MHz, $CDCl_3$); 7.54 (1H, s, H-5''), 7.28 - 7.26 (1H, m, ArH), 7.23 (1H, d, J = 3.0 Hz, ArH), 7.10 (1H, s, H-7), 7.03 (1H, t, J = 4.0 Hz, ArH), 6.96 (1H, d, J = 8.5 Hz, H-5), 6.54 (1H, d, J = 9.0 Hz, H-4), 4.80 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.4 (C-2'), 45.9 (C-1'), 107.9 (C-4), 114.2 (C-7), 118.8 (C-5), 119.3 (C-5''), 120.6 (ArC), 122.2 (ArC), 123.3 (ArCH), 124.2 (ArCH), 126.5 (ArCH), 131.3 (ArC), 137.5 (ArC), 142.0 (ArC), 142.8 (Ar(OCF_3)), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{16}H_{13}F_3N_5OS_2$ requires 412.05, found 412.05.

^{1}H NMR

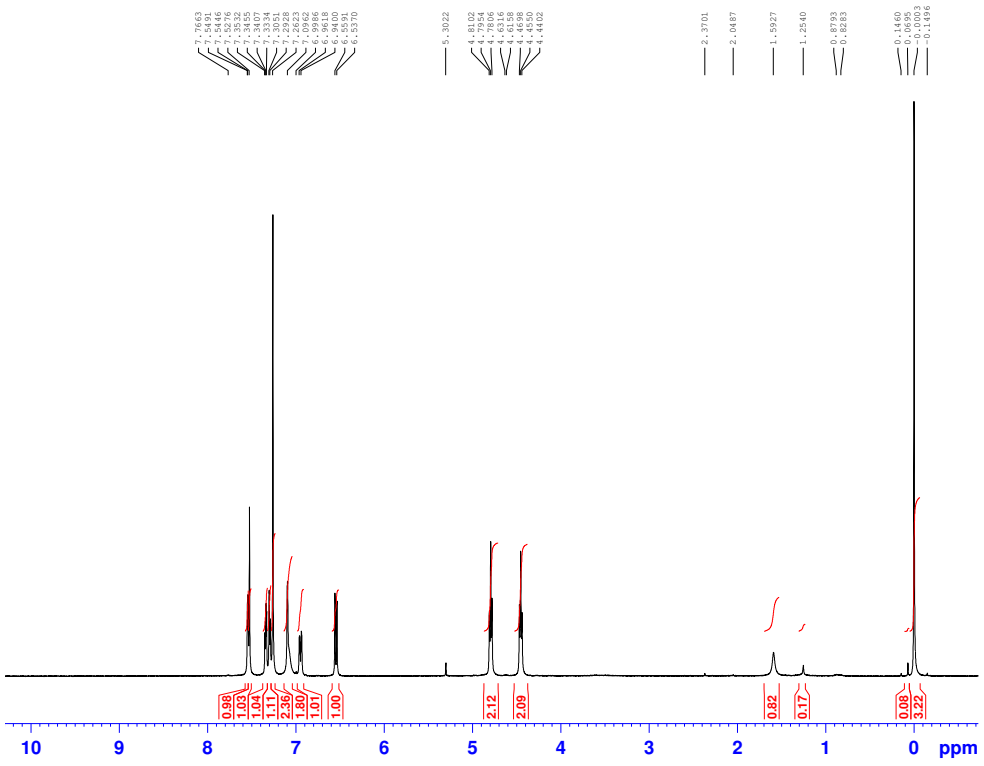


3-(2-(4-(Thiophen-3-yl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5ar



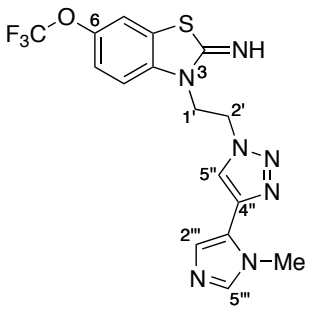
Using the general procedure; to a solution of azide **6** (0.20 g, 0.67 mmol, 1.0 equiv.) and 3-ethynylthiophene (0.1 mL, 1.00 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.3 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(thiophen-3-yl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5ar**, 0.15 g, 0.37 mmol, 55 %) as an off white solid; **R_f** 0.17 (100 % EtOAc), **m.p.** 185 - 188 °C; **IR** ν_{max}/cm^{-1} 3246, 3081, 1615, 1585, 1483, 1258; **^{1}H NMR** (400MHz, $CDCl_3$); 7.55 (1H, d, J = 2.0 Hz, ArH), 7.53 (1H, s, H-5''), 7.35 - 7.33 (1H, m, ArH), 7.30 (1H, d, J = 5.0 Hz, ArH), 7.09 (1H, s, H-7), 6.95 (1H, d, J = 8.5 Hz, H-5), 6.55 (1H, d, J = 9.0 Hz, H-4), 4.80 (2H, t, J = 6.0 Hz, H-1'), 4.46 (2H, t, J = 6.0 Hz, H-2'); **^{13}C NMR** (100MHz, $CDCl_3$); 42.5 (C-2'), 45.8 (C-1'), 108.0 (C-4), 114.2 (C-7), 118.8 (C-5), 119.6 (C-5''), 120.2 (ArCH), 120.6 (ArC), 122.2 (ArC), 124.7 (ArCH), 125.3 (ArCH), 130.3 (ArC), 137.5 (ArC), 142.8 (Ar(OCF_3)), 143.2 (ArC), 159.8 (ArC); **MS** m/z $[M+H]^+$ $C_{16}H_{13}F_3N_5OS_2$ requires 412.05, found 412.05.

^{1}H NMR



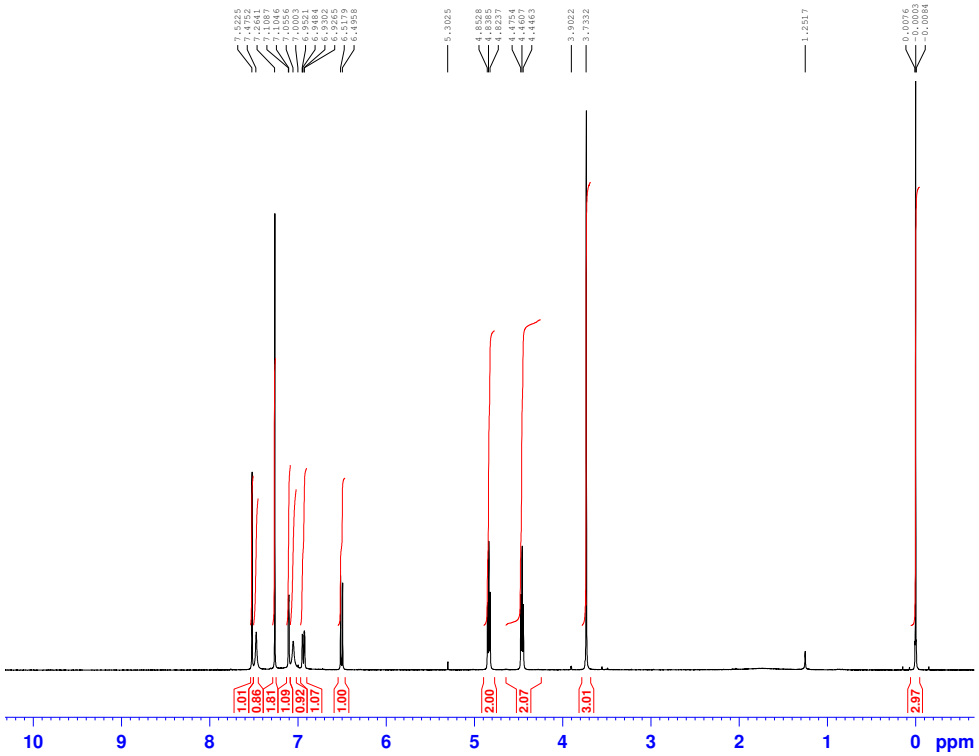
3-(2-(4-(1-Methyl-1*H*-imidazol-5-yl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine

5as

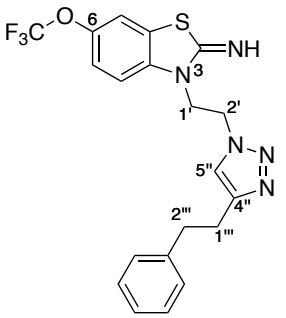


Using the general procedure; to a solution of azide **6** (0.20 g, 0.66 mmol, 1.0 equiv.) and 5-ethynyl-1-methyl-1H-imidazole (0.1 mL, 0.99 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.3 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 9:1 DCM:MeOH to yield 3-(2-(4-(1-methyl-1*H*-imidazol-5-yl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5as**, 0.18 g, 0.44 mmol, 67 %) as an off white solid; **R_f** 0.52 (9:1 DCM:MeOH), **m.p.** 220 - 225 °C; **IR** ν_{max}/cm^{-1} 3161, 2958, 1626, 1585, 1484, 1267; **^{1}H NMR** (400MHz, $CDCl_3$); 7.52 (1H, s, H-5''), 7.48 (1H, s, H-2'''), 7.11 (1H, d, J =1.5 Hz, H-7), 7.06 (1H, s, H-5'''), 6.94 (1H, dd, J = 1.5 Hz and 9.0 Hz, H-5), 6.51 (1H, d, J = 9.0 Hz, H-4), 4.84 (2H, t, J = 5.5 Hz, H-1'), 4.47 (2H, t, J = 6.0 Hz, H-2'), 3.73 (3H, s, $N(CH_3)$); **^{13}C NMR** (100MHz, $CDCl_3$); 33.2 ($N(CH_3)$), 43.5 (C-2'), 46.8 (C-1'), 108.7 (C-4), 115.4 (C-7), 119.7 (C-5), 122.4 (C-5''), 123.4 (ArC), 129.1 (C-5'''), 138.5 (C-2'''), 160.7 (ArC); **MS** m/z $[M+H]^+$ $C_{16}H_{15}F_3N_7OS$ requires 410.10, found 410.10.

^{1}H NMR

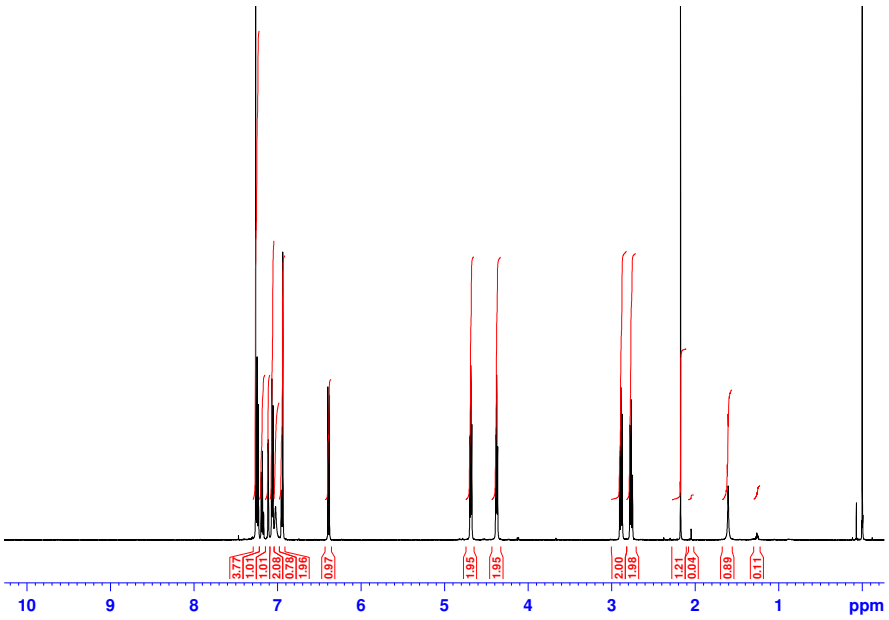


3-(2-(4-Phenylethyl-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5at

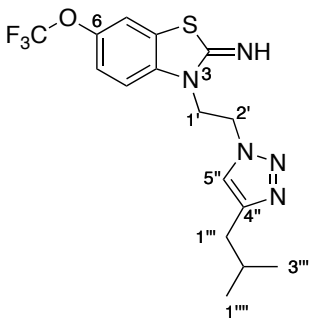


Using the general procedure; to a solution of azide **6** (0.18 g, 0.59 mmol, 1.0 equiv.) and 4-phenyl-1-butyne (0.1 mL, 0.89 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.6 mL 1M $CuSO_4$ (aq) and 1.2 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-phenylethyl-1,2,3-triazolyl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5at**, 0.12 g, 0.28 mmol, 47 %) as an off-white solid; **R_f** 0.13 (100 % EtOAc), **m.p.** 153 - 157 °C; **IR** ν_{max}/cm^{-1} 3263, 3030, 1614, 1585, 1484, 1260; **^{1}H NMR** (500MHz, $CDCl_3$); 7.25 (2H, appt, J = 7.5 Hz, ArH), 7.19 (1H, t, J = 6.0 Hz, ArH), 7.11 (1H, s, H-7), 7.07 (2H, d, J = 7.0 Hz, ArH), 7.03 (1H, bs, NH), 6.96 - 6.94 (2H, m, H-5 and H-5''), 6.39 (1H, d, J = 9.0 Hz, H-4), 4.69 (2H, t, J = 5.5 Hz, H-1'), 4.39 (2H, t, J = 6.0 Hz, H-2'), 2.89 (2H, t, J = 7.5 Hz, H-2'''), 2.77 (2H, t, J = 8.5 Hz, H-1'''); **^{13}C NMR** (125MHz, $CDCl_3$); 26.1 (C-2'''), 34.4 (C-1'''), 42.8 (C-2'), 45.8 (C-1'), 107.9 (C-4), 114.1 (C-7), 118.1 (ArC), 118.8 (C-5), 122.1 (C-5''), 123.2 (ArC), 125.1 (ArCH), 127.3 (ArCH), 127.4 (ArCH), 137.7 (ArC), 140.0 (ArC), 142.7 (Ar(OCF_3)) 146.6 (ArC), 159.67 (ArC); **MS** m/z $[M+H]^+$ $C_{20}H_{19}F_3N_5OS$ requires 434.13 found 434.13.

^{1}H NMR

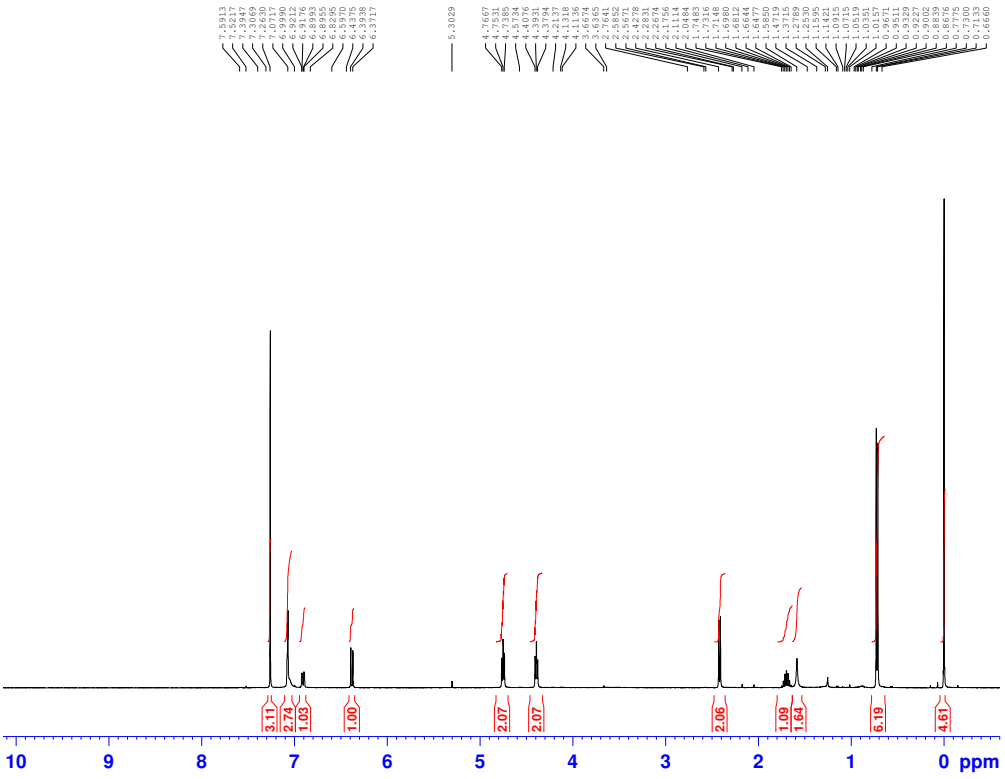


3-(2-(4-Isobutyl-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5au

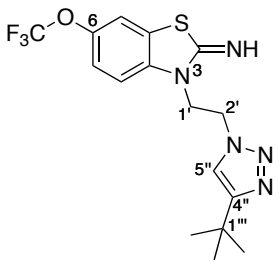


Using the general procedure; to a solution of azide **6** (0.14 g, 0.48 mmol, 1.0 equiv.) and 4-methyl-1-pentyne (0.1 mL, 0.72 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 1.0 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-isobutyl-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5au**, 0.18 g, 0.47 mmol, 98 %) as an off-white solid; $\mathbf{R_f}$ 0.19 (100 % EtOAc), **m.p.** 165 -170 °C; **IR** ν_{max}/cm^{-1} 3237, 3065, 2955, 1580, 1485, 1263; **^{1}H NMR** (400MHz, $CDCl_3$); 7.07 (2H, s, H-7 and H-5''), 6.91 (1H, dd, J = 1.5 Hz and 9.0 Hz, H-5), 6.38 (1H, d, J = 9.0 Hz, H-4), 4.76 (2H, t, J = 5.5 Hz, H-1'), 4.40 (1H, t, J = 6.0 Hz, H-2'), 2.42 (2H, d, J = 6.0 Hz, H-1'''), 1.70 (1H, sept, J = 6.5 Hz, H-2'''), 0.72 (6H, d, J = 6.5 Hz, H-3''' and H-1''''); **^{13}C NMR** (100MHz, $CDCl_3$); 21.9 (C-1'''' and C-3'''), 28.5 (C-2'''), 34.4 (C-1'''), 44.0 (C-2'), 46.7 (C-1'), 108.9 (C-4), 115.1 (C-7), 119.8 (C-5), 122.5 (C-5''); **MS** m/z $[M+H]^+$ $C_{16}H_{19}F_3N_5OS$ requires 386.13, found 386.13.

^{1}H NMR

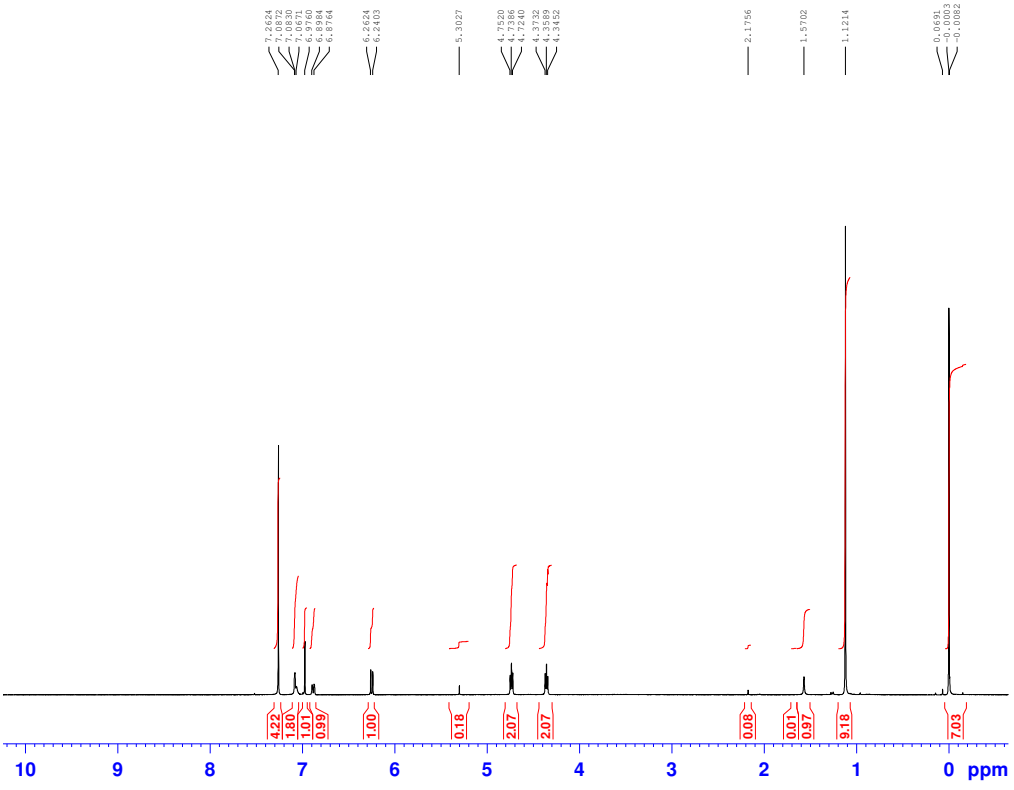


3-(2-(4-(*tert*-Butyl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5av

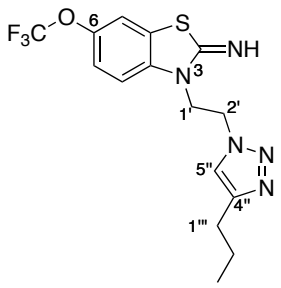


Using the general procedure; to a solution of azide **6** (0.16 g, 0.53 mmol, 1.0 equiv.) and 3,3-dimethyl-1-butyne (0.1 mL, 0.80 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 1.1 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-(*tert*-butyl)-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5av**, 0.13 g, 0.34 mmol, 64 %) as a pale yellow solid; $\mathbf{R_f}$ 0.13 (100 % EtOAc), **m.p.** 150 - 154 °C; **IR** ν_{max}/cm^{-1} 3256, 3068, 2979, 1605, 1580, 1484, 1258; **^{1}H NMR** (400MHz, $CDCl_3$); 7.09 (1H, s, H-7), 6.98 (1H, s, H-5''), 6.89 (1H, d, J = 9.0 Hz, H-5), 6.25 (1H, d, J = 9.0 Hz, H-4), 4.74 (2H, t, J = 5.5 Hz, H-1'), 4.36 (2H, t, J = 5.5 Hz, H-2'), 1.12 (9H, s, $ArC(CH_3)_3$); **^{13}C NMR** (100MHz, $CDCl_3$); 29.1 ($ArC(\mathbf{C}H_3)_3$), 42.9 (C-2'), 45.6 (C-1'), 107.7 (C-4), 114.0 (C-7), 118.1 (ArC), 118.7 (C-5), 118.8 (C-5''), 120.7 (ArC), 123.2 (ArC), 137.7 (ArC), 142.6 ($Ar(OCF_3)$), 157.1 (ArC), 159.6 (ArC); **MS** m/z $[M+H]^+$ $C_{16}H_{19}F_3N_5OS$ requires 386.13, found 386.13.

^{1}H NMR

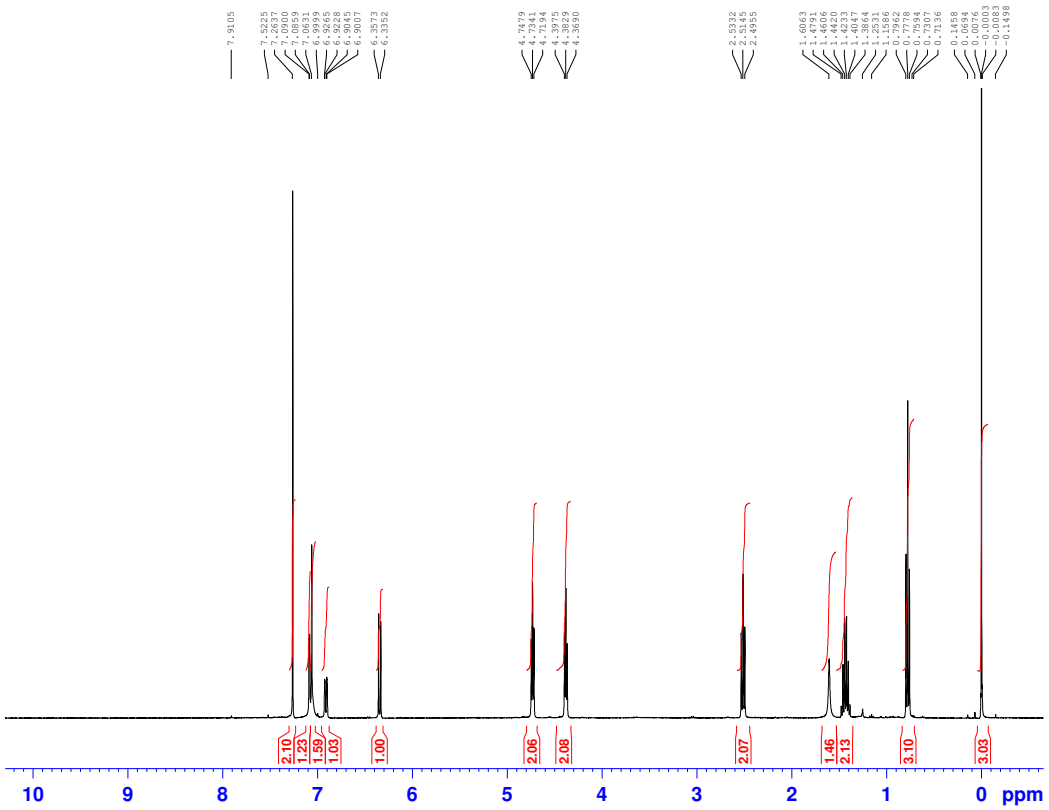


3-(2-(4-Propyl-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5aw

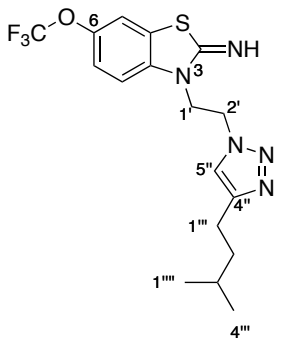


Using the general procedure; to a solution of azide **6** (0.16 g, 0.53 mmol, 1.0 equiv.) and 1-pentyne (0.1 mL, 0.79 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 1.1 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-propyl-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5aw**, 0.09 g, 0.23 mmol, 44 %) as a pale yellow solid; $\mathbf{R_f}$ 0.14 (100 % EtOAc), **m.p.** 134 - 138 °C; **IR** ν_{max}/cm^{-1} 3334, 3072, 2961, 2933, 1602, 1580, 1484, 1257; **^{1}H NMR** (400MHz, $CDCl_3$); 7.09 (1H, d, J = 1.5 Hz, H-7), 7.06 (1H, s, H-5''), 6.92 (1H, dd, J = 1.5 Hz and 9.0 Hz, H-5), 6.35 (1H, d, J = 9.0 Hz, H-4), 4.74 (2H, t, J = 5.5 Hz, H-1'), 4.39 (2H, t, J = 6.0 Hz, H-2'), 2.52 (2H, t, J = 7.5 Hz, H-1'''), 1.44 (2H, sext, J = 7.5 Hz, H-2'''), 0.78 (3H, t, J = 7.5 Hz, H-3'''); **^{13}C NMR** (100MHz, $CDCl_3$); 13.4 (C-3'''), 22.7 (C-2'''), 27.3 (C-1'''), 43.9 (C-2'), 46.7 (C-1'), 108.8 (C-4), 115.1 (C-7), 119.8 (C-5), 121.9 (C-5''), 123.0 (ArC), 138.7 (ArC), 143.7 (ArC), 148.6 (ArC); **MS** m/z $[M+H]^+$ $C_{15}H_{16}F_3N_5OS$ requires 372.11, found 372.11.

^{1}H NMR

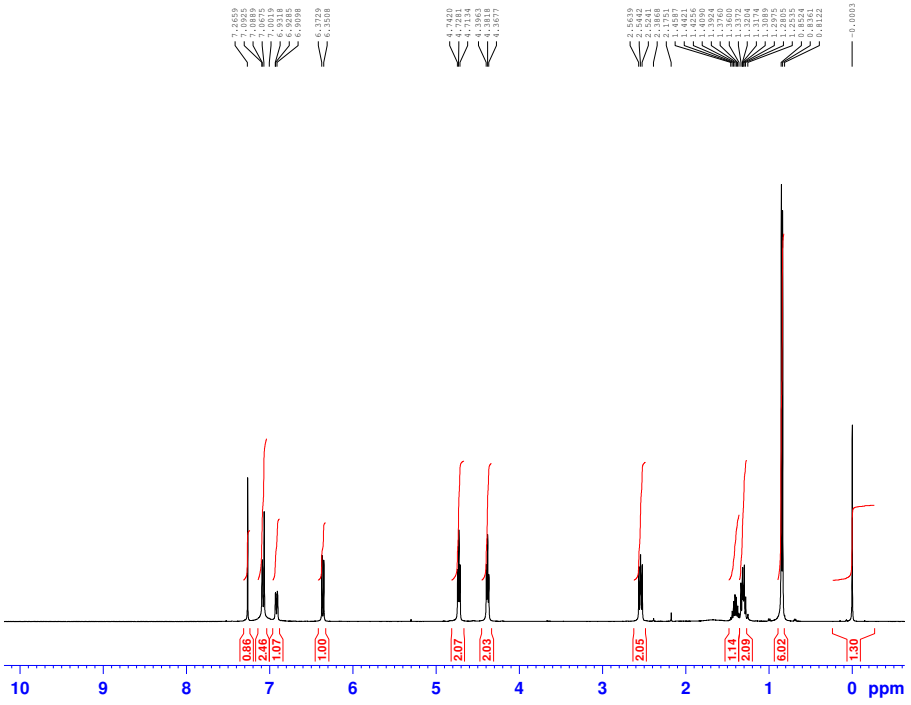


3-(2-(4-Isopentyl-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5ax

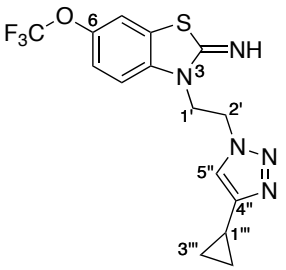


Using the general procedure; to a solution of azide **6** (0.16 g, 0.54 mmol, 1.0 equiv.) and 5-methyl-1-hexyne (0.1 mL, 0.81 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 1.1 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-isopentyl-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5ax**, 0.14 g, 0.34 mmol, 63 %) as a pale yellow solid; $\mathbf{R_f}$ 0.11 (100 % EtOAc), **m.p.** 126 - 129 °C; **IR** ν_{max}/cm^{-1} 3232, 3072, 2958, 1602, 1581, 1484, 1257; **^{1}H NMR** (400MHz, $CDCl_3$); 7.09 (1H, s, H-7), 7.07 (1H, s, H-5''), 6.92 (1H, d, J = 9.0 Hz, H-5), 6.36 (1H, d, J = 9.0 Hz, H-4), 4.73 (2H, t, J = 5.5 Hz, H-1'), 4.39 (2H, t, J = 6.0 Hz, H-2'), 2.54 (2H, t, J = 8.0 Hz, H-1'''), 1.46 - 1.36 (1H, m, H-3'''), 1.34 - 1.28 (2H, m, H-2'''). 0.85 (6H, d, J = 6.5 Hz, H-4''' and H-1''''); **^{13}C NMR** (100MHz, $CDCl_3$); 22.2 (C-4''' and C-1''''), 26.3 (C-1'''), 37.4 (C-2''' and C-3'''), 42.8 (C-2'), 45.7 (C-1'), 107.9 (C-4), 114.0 (C-7), 118.1 (ArC), 118.7 (C-5), 120.7 (C-5''), 122.1 (ArC), 137.6 (ArC), 142.7 (Ar(OCF_3)), 147.9 (ArC), 159.7 (ArC); **MS** m/z $[M+H]^+$ $C_{17}H_{21}F_3N_5OS$ requires 400.14, found 400.14.

^{1}H NMR

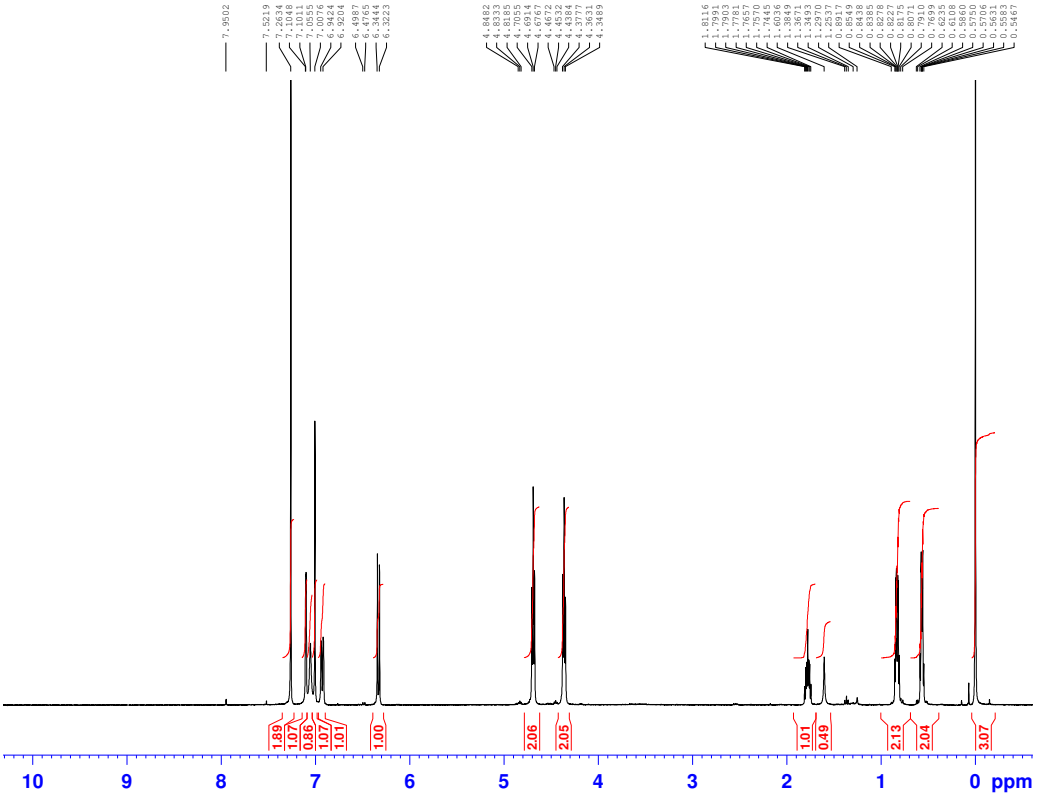


3-(2-(4-Cyclopropyl-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5ay

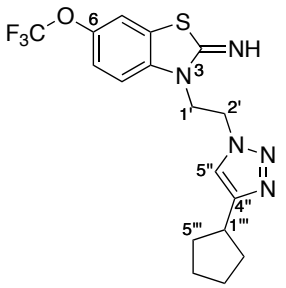


Using the general procedure; to a solution of azide **6** (0.20 g, 0.66 mmol, 1.0 equiv.) and cyclopropylacetylene (0.1 mL, 0.99 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.3 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-cyclopropyl-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5ay**, 0.16 g, 0.44 mmol, 67 %) as a pale yellow solid; $\mathbf{R_f}$ 0.10 (100 % EtOAc), **m.p.** 149 - 152 °C; **IR** ν_{max}/cm^{-1} 3220, 3089, 2950, 1601, 1580, 1484, 1256; **^{1}H NMR** (400MHz, $CDCl_3$); 7.10 (1H, s, H-7), 7.01 (1H, s, H-5''), 6.93 (1H, d, J = 9.0 Hz, H-5), 6.33 (1H, d, J = 9.0 Hz, H-4), 4.70 (2H, t, J = 5.5 Hz, H-1'), 4.37 (2H, t, J = 6.0 Hz, H-2'), 1.78 (1H, tt, J = 5.0 Hz and 13.5 Hz, H-1'''), 0.83 (2H, dt, J = 4.5 Hz and 15.0 Hz, H-2''' and H-3'''), 0.57 (2H, dt, J = 4.5 Hz and 11.0 Hz, H-2''' and H-3'''); **^{13}C NMR** (100MHz, $CDCl_3$); 5.3 (C-1'''), 6.5 (C-2''' and C-3''''), 42.7 (C-2'), 45.7 (C-1'), 107.8 (C-4), 114.1 (C-7), 118.5 (C-5), 119.8 (C-5''), 120.7 (ArC), 122.0 (ArC), 137.6 (ArC), 142.7 (Ar(OCF_3)), 149.7 (ArC), 159.6 (ArC); **MS** m/z $[M+H]^+$ $C_{15}H_{15}F_3N_5OS$ requires 370.10, found 370.10.

^{1}H NMR

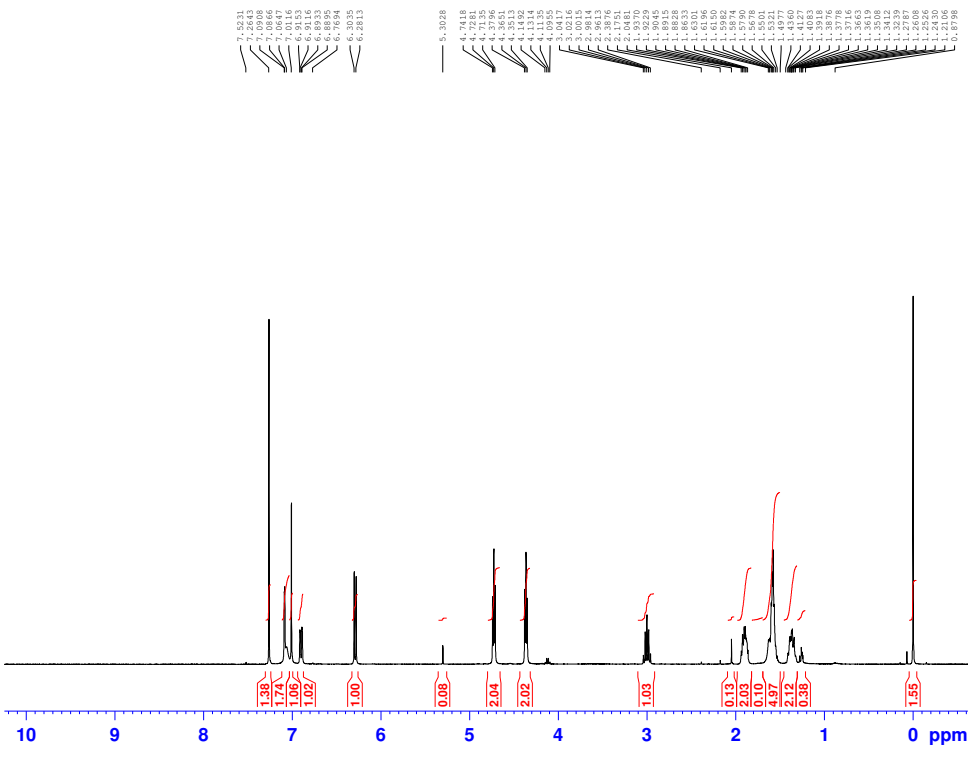


3-(2-(4-Cyclopentyl-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5az

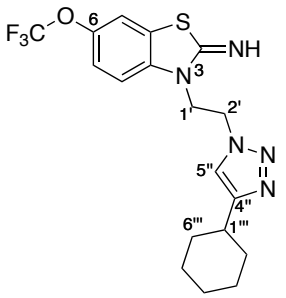


Using the general procedure; to a solution of azide **6** (0.21 g, 0.68 mmol, 1.0 equiv.) and cyclopentylacetylene (0.1 mL, 1.02 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.7 mL 1M $CuSO_4$ (aq) and 1.4 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-cyclopentyl-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5az**, 0.16 g, 0.40 mmol, 59 %) as an off white solid; **R_f** 0.13 (100 % EtOAc), **m.p.** 174 - 179 °C; **IR** ν_{max}/cm^{-1} 3248, 3078, 2948, 1600, 1579, 1484, 1261; **^{1}H NMR** (400MHz, $CDCl_3$); 7.09 (1H, s, H-7), 7.01 (1H, s, H-5''), 6.91 (1H, dd, J = 1.5 Hz and 9.0 Hz, H-5). 6.29 (1H, d, J = 9.0 Hz, H-4), 4.73 (2H, t, J 5.5 Hz, H-1'), 4.37 (2H, t, J = 6.0 Hz, H-2'), 3.01 (1H, quin, J = 8.0 Hz, H-1'''), 1.94 - 1.86 (2H, m, H-2''' and H-5'''), 1.63 - 1.53 (4H, m, H-3''' and H-4'''), 1.44 - 1.32 (2H, m, H-2''' and H-5'''); **^{13}C NMR** (100MHz, $CDCl_3$); 23.9 (C-3''' and C-4'''), 32.1 (C-2''' and C-5'''), 35.4 (C-1'''), 42.9 (C-2'), 45.7 (C-1'), 107.8 (C-4), 114.0 (C-7), 118.8 (C-5), 119.8 (C-5''), 120.7 (ArC), 121.9 (ArC), 137.7 (ArC), 142.7 (Ar(OCF_3)), 152.2 (ArC), 159.6 (ArC); **MS** m/z $[M+H]^+$ $C_{17}H_{19}F_3N_5Os$ requires 398.13, found 198.13.

^{1}H NMR

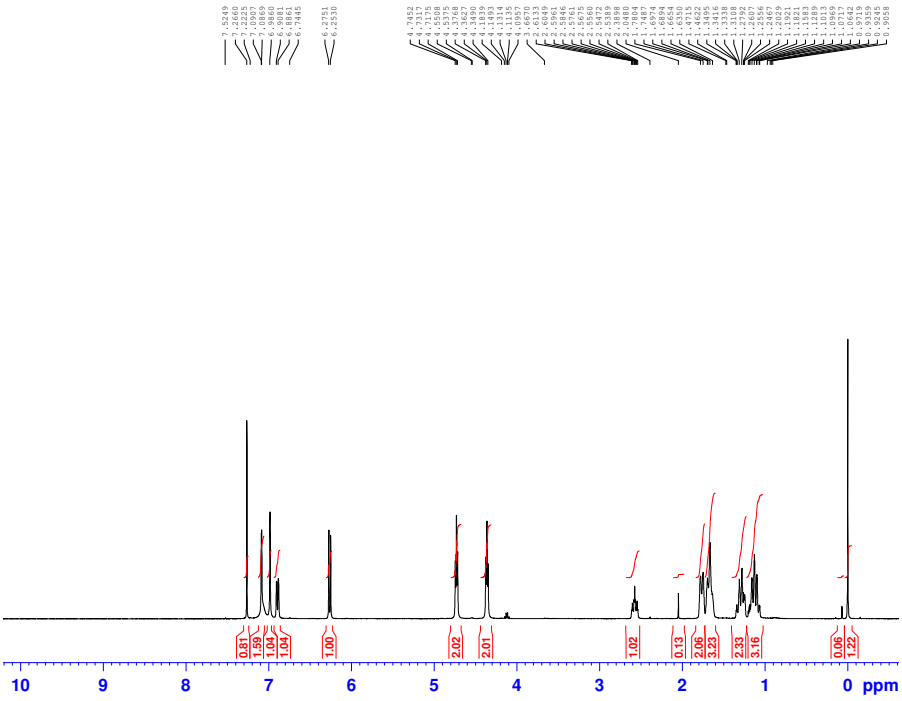


3-(2-(4-Cyclohexyl-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine 5aaa

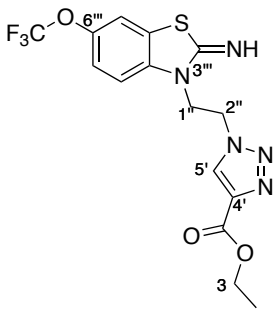


Using the general procedure; to a solution of azide **6** (0.23 g, 0.75 mmol, 1.0 equiv.) and cyclohexylacetylene (0.2 mL, 1.12 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.8 mL 1M $CuSO_4$ (aq) and 1.5 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield 3-(2-(4-cyclohexyl-1,2,3-triazol-1-yl)ethyl)-6-(trifluoromethoxy)benzothiazol-2-imine (**5aaa**, 0.17 g, 0.41 mmol, 55 %) as a pale yellow solid; $\mathbf{R_f}$ 0.15 (100 % EtOAc), **m.p.** 178 - 182 °C; **IR** ν_{max}/cm^{-1} 3220, 3028, 2925, 1581, 1483, 1254; **^{1}H NMR** (400MHz, $CDCl_3$); 7.09 (1H, s, H-7), 6.99 (1H, s, H-5''), 6.90 (1H, d, J = 9.0 Hz, H-5), 6.27 (1H, d, J = 9.0 Hz, H-4), 4.74 (2H, t, J = 5.5 Hz, H-1'), 4.37 (2H, t, J = 5.5 Hz, H-2'), 2.58 (1H, ttt, J = 3.5 Hz and 11.5 Hz, H-1'''), 1.78 - 1.75 (2H, m, H-2''' and H-6'''), 1.70 -1.64 (3H, m, H-3''', H-4''' and H-5'''), 1.35 - 1.25 (2H, m, H-2''' and H-6'''), 1.20 - 1.06 (3H, m, H-3''', H-4''' and H-5'''); **^{13}C NMR** (100MHz, $CDCl_3$); 25.1 (C-3''', C-4''' and C-5'''), 31.9 (C-2''' and C-6'''), 34.0 (C-1'''), 42.9 (C-2'), 45.7 (C-1'), 107.8 (C-4), 114.0 (C-7), 118.1 (ArC), 118.8 (C-5), 119.6 (C-5''), 120.6 (ArC), 121.9 (ArC), 137.7 (ArC), 142.6 (Ar(OCF_3)), 153.1 (ArC), 159.6 (ArC); **MS** m/z $[M+H]^+$ $C_{18}H_{21}F_3N_5OS$ requires 412.14, found 412.14.

^{1}H NMR



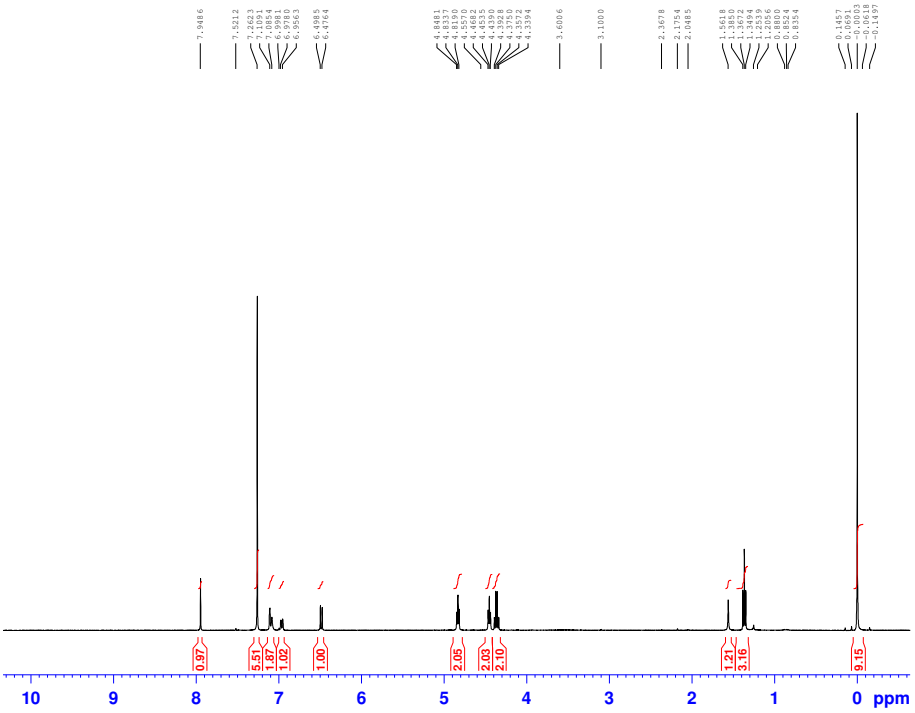
Ethyl 1-(2-(2-Imino-6-(trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazole-4-carboxylate 5aab



Using the general procedure; to a solution of azide **6** (0.15 g, 0.48 mmol, 1.0 equiv.) and ethyl propiolate (0.1 mL, 0.72 mmol, 1.5 equiv.) in 10.0 mL H_2O and 10.0 mL THF heated to 20 °C was added 0.5 mL 1M $CuSO_4$ (aq) and 1.0 mL sodium ascorbate (aq., 1M, freshly prepared) dropwise. This was stirred at 20 °C for 2 h. After work-up the crude was column purified using 100 % EtOAc to yield ethyl 1-(2-(2-imino-6-(trifluoromethoxy)benzothiazol-3-yl)ethyl)-1,2,3-triazole-4-carboxylate (**5aab**, 0.12 g, 0.29 mmol, 61 %) as a pale yellow solid; $\mathbf{R_f}$ 0.15 (100 % EtOAc), **m.p.** 159 - 163 °C

IR ν_{max}/cm^{-1} 3276, 3043, 2979, 1721, 1631, 1583, 1485, 1261; **^{1}H NMR** (400MHz, $CDCl_3$); 7.95 (1H, s, H-5'), 7.11 (1H, s, H-7'''), 6.97 (1H, d, J = 8.5 Hz, H-5'''), 6.49 (1H, d, J = 9.0 Hz, H-4'''), 4.84 (2H, t, J = 6.0 Hz, H-1''), 4.46 (2H, t, J = 6.0 Hz, H-2''), 4.37 (2H, q, J = 7.0 Hz, H-3), 1.37 (3H, t, J = 7.0 Hz, H-4); **^{13}C NMR** (100MHz, $CDCl_3$); 14.2 (C-4), 43.3 (C-2''), 47.2 (C-1''), 61.4 (C-3), 108.7 (C-4'''), 115.4 (C-7'''), 119.9 (C-5'''), 121.7 (ArC), 123.4 (ArC), 128.6 (C-5'), 138.4 (ArC), 140.4 (ArC), 143.9 (Ar(OCF_3)), 160.4 (ArC), 160.8 (ArC); **MS** m/z $[M+H]^+$ $C_{15}H_{15}F_3N_5O_3S$ requires 402.09, found 402.08.

^{1}H NMR



Screening data

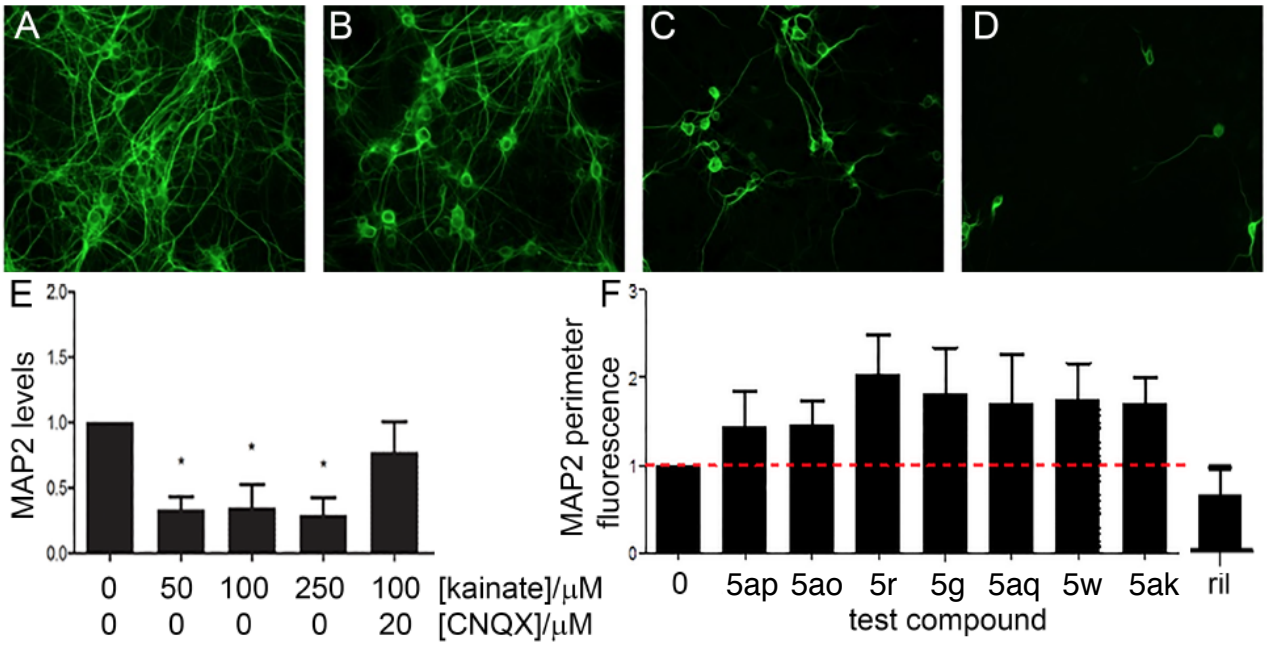


Figure 2. Primary cortical neurons treated with kainate show a loss in MAP2 fluorescence that is partly reversed with riluzole derivatives Primary cortical neurons were treated for 18 hours with vehicle (A) or kainate (50, 100 or 250 mM; B-D) then fixed and stained for MAP2. Pictures show loss of neurofilaments without significant cell death with 50 or 100 mM kainate. The loss of neurofilament protein MAP2 assessed by Western Blotting is represented graphically in E, where the AMPA antagonist CNQX (20 mM) reverses kainate-induced MAP2 loss. Panel F represents experiments where primary cortical neurons were pretreated with riluzole derivatives (1 μM) followed by 18 hours treatment with 100 μM kainate. Cells were fixed and stained for MAP2 with 10 images per experimental condition analysed per n using Volocity perimeter analysis. n=4. For data presentation, the kainate-induced loss is normalised to 1 representing an approximate 70% decrease from untreated control values (not shown, but refer to panel E for comparison). Test compounds which led to MAP2 fluorescent levels above the red dashed line demonstrate the ability of compounds to partially reverse of kainate-induced MAP2 loss. The parent, riluzole, is not effective in this assay

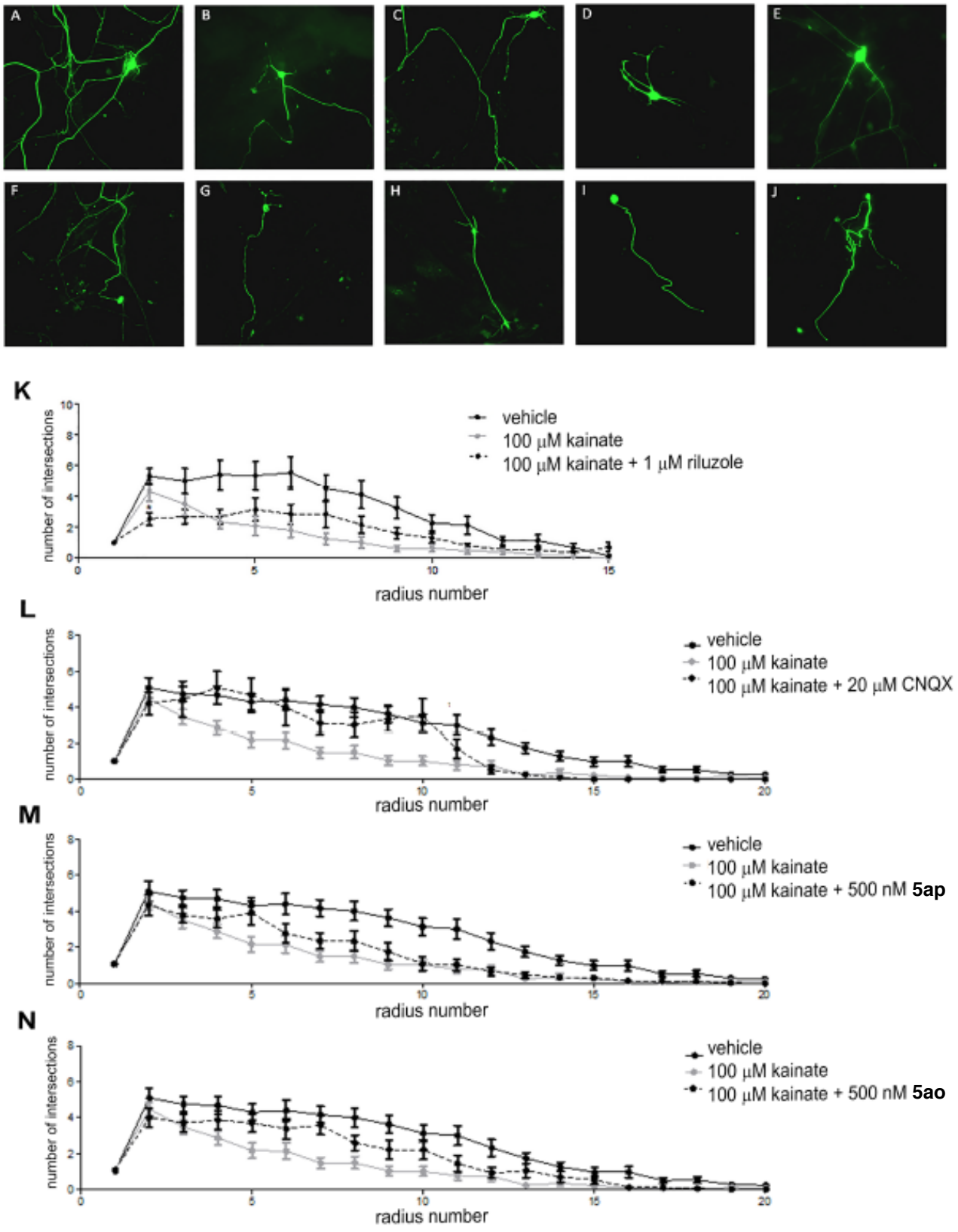


Figure 3. Riluzole derivatives can preserve motor neuron morphology in response to kainate. Primary motor neurons were treated with A) vehicle or B) 100 μM kainate alone or treated with kainate following pre-treatment with C) the AMPA antagonist CNQX, D) 500 nM **5ap**, E) 500 nM **5ao**, F) 1 μM **5g**, G) 500 nM **5aq**, H) 1 μM **5w**, or I) 1 μM **5ak**. Cells were fixed and stained for SMI-32. n=3. K shows a representative pooled

analysis, where riluzole (1 mM, K), CNQX (L), **5ao** (M), **5ap** (N) significantly increased the number of neuronal processes extending between 5-10 radii compared to kainate treatment: in the graph. For each figure the black line represents vehicle treated control, the grey represents agonist treatment and the dashed line represents agonist treatment in the presence of riluzole. There was significant protection of kainate-induced changes by riluzole, CNQX, **5ao** and **5ap** (two-way ANOVA, with a Bonferroni post-hoc test. $p<0.05$. $n=4$).

References

1. Heidempergher, F.; Pillan, A.; Pinciroli, V.; Vaghi, F.; Arrigoni, C.; Bolis, G.; Caccia, C.; Dho, L.; McArthur, R.; Varasi, M. *J. Med. Chem.* **1997**, *40*, 3369–3380.
2. Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797–3800.